STIC Search

File 350:Derwent WPIX 1963-2001/UD,UM &UP=200170
File 344:CHINESE PATENTS ABS APR 1985-2001/Oct
File 347:JAPIO OCT 1976-2001/JUL(UPDATED 011105)
File 371:French Patents 1961-2001/BOPI 200147

Set	Items	Description
S1	35	AU="EDWARDS D A"
S2	10	AU="EDWARDS DAVID ALAN"
S3	3	AU="BATYCKY R P"
S4	55	AU="JOHNSTON L":AU="JOHNSTON L W"
S5	20782	AEROSOL
S6	0	S4 AND S5
S7	502	BIOACTIVE()AGENT?
S8	**1**	**S1:S4 AND (S5 OR S7)**
S9	**3**	**S3 NOT S8**

8/7/1 (Item 1 from file: 350)
DIALOG(R)File 350:Derwent WPIX

013052674
WPI Acc No: 2000-224529/200019
Production of spray dried particles for delivering active agent to respiratory tract by spraying drying bioactive agent, phospholipid and co-solvent
Patent Assignee: ADVANCED INHALATION RES INC (ADIN-N)
Inventor: EDWARDS D A ; HRKACH J S
Number of Countries: 088 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200010541	A1	20000302	WO 99US19306	A	19990825	200019	B
AU 9957842	A	20000314	AU 9957842	A	19990825	200031	
EP 1107743	A1	20010620	EP 99945175	A	19990825	200135	
			WO 99US19306	A	19990825		

Priority Applications (No Type Date): US 9897796 P 19980825
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200010541	A1	E	34	A61K-009/72	

Designated States (National): AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW

AU 9957842	A		A61K-009/72	Based on patent WO 200010541
EP 1107743	A1	E	A61K-009/72	Based on patent WO 200010541

Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

Abstract (Basic): WO 200010541 A1
NOVELTY - Production of spray-dried particles comprises:
(1) combining a bioactive agent , a phospholipid and a co-solvent, the co-solvent including an aqueous solvent and an organic solvent, to form a mixture and
(2) spray-drying the mixture
ACTIVITY - Respiratory.
Human growth hormone was spray-dried in an aqueous/ethanol co-solvent mixture with DPPC. A 70/30 ethanol/aqueous co-solvent (vol/vol) and solute concentrations (combined hGH and DPPC) of 0.1% w/v were used. The pH was 7.4 (NaPO4 buffer). 60/40 hGH/DPPC and 80/20 hGH/DPPC particles were prepared. The tap densities ranged from 0.02 to

0.04 g/cc with mean geometric diameters of 7-8 mum. This gave aerodynamic diameters in the range of 1-3 mum, ideal for inhalation.
USE - The spray-dried particles can be administered to the respiratory tract (claimed) and can be delivered to the pulmonary system.
ADVANTAGE - The spray-dried particles have increased protein stability.
pp; 34 DwgNo 0/0
Derwent Class: B04; B07
International Patent Class (Main): A61K-009/72
International Patent Class (Additional): A61K-009/14

9/26/1 (Item 1 from file: 350)
DIALOG(R)File 350:Derwent WPIX
(c) 2001 Derwent Info Ltd. All rts. reserv.
013773374
WPI Acc No: 2001-257585/200126
Use of amino acids to form porous particles for drug delivery to the pulmonary system with a tap density of less than 0.4 g/ml

9/26/2 (Item 2 from file: 350)
DIALOG(R)File 350:Derwent WPIX
(c) 2001 Derwent Info Ltd. All rts. reserv.
013750738
WPI Acc No: 2001-234967/200124
Particles comprising an active agent, a carboxylate moiety, a phospholipid and multivalent salt, for delivery to the pulmonary system

9/26/3 (Item 3 from file: 350)
DIALOG(R)File 350:Derwent WPIX
(c) 2001 Derwent Info Ltd. All rts. reserv.
012975322
WPI Acc No: 2000-147171/200013
Aggregated particles for drug delivery to the pulmonary system comprise a therapeutic, diagnostic or prophylactic agent and a surfactant

File 348:EUROPEAN PATENTS 1978-2001/NOV W04
File 349:PCT FULLTEXT 1983-2001/UB=20011129,UT=20011122

Set	Items	Description
S1	40	AU="EDWARDS DAVID":AU="EDWARDS DAVID ALAN"
S2	6	AU="BATYCKY RICHARD P"
S3	**2**	**S1 AND S2**
S4	3	S1:S2 AND BIOACTIVE
S5	**3**	**S4 NOT S3**

3/6,AB/2 (Item 1 from file: 349)
00535551
LARGE POROUS PARTICLES EMITTED FROM AN INHALER
GRANDES PARTICULES POREUSES EMISES PAR UN INHALATEUR
Publication Language: English
Fulltext Availability:
Detailed Description
Claims
Fulltext Word Count: 19218
Publication Year: 1999
DIALOG(R)File 349:(c) 2001 WIPO/Univentio. All rts. reserv.
English Abstract
Particles incorporating a surfactant and/or a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a

See next page

3/3,AB/2
DIALOG(R)File 349:PCT FULLTEXT

00535551
LARGE POROUS PARTICLES EMITTED FROM AN INHALER
GRANDES PARTICULES POREUSES EMISES PAR UN INHALATEUR
Patent Applicant/Assignee:
ADVANCED INHALATION RESEARCH INC,
Inventor(s):
EDWARDS David A,
BATYCKY Richard P,
CAPONETTI Giovanni,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9966903 A2 19991229
Application: WO 99US14074 19990622 (PCT/WO US9914074)
Priority Application: US 9890454 19980624
Designated States: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 19218
English Abstract
Particles incorporating a surfactant and/or a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a charged molecule of opposite charge for drug delivery to the pulmonary system, and methods for their synthesis and administration are provided. In a preferred embodiment, the particles are made of a biodegradable material and have a tap density less than 0.4 g/cm3 and a mass mean diameter between 5 mum and 30 mum, which together yield an aerodynamic diameter of the particles of between approximately one and five microns. The particles may be formed of biodegradable materials such as biodegradable polymers. For example, the particles may be formed of poly(lactic acid) or poly(glycolic acid) or copolymers thereof. Alternatively, the particles may comprise a therapeutic, prophylactic or diagnostic agent and a material selected from the group consisting of surfactant and a molecule having a charge opposite to the charge of the agent and forming a complex thereto. The particles have a tap density less than 0.4 g/cm3 and a mass mean diameter between 5 mum and 30 mum. Exemplary surfactants include phosphoglycerides such as dipalmitoyl phosphatidylcholine (DPPC). The particles are administered to the respiratory tract to permit systemic or local delivery of a wide variety of therapeutic agents. Aggregation of particles before or during administration to the respiratory tract results in particles having an aerodynamic diameter larger than that of the fully dispersed particles. Aerodynamic diameters between three and five microns are advantageous for delivery to the central airways.

charged molecule of opposite charge for drug delivery to the pulmonary system, and methods for their synthesis and administration are provided. In a preferred embodiment, the particles are made of a biodegradable material and have a tap density less than 0.4 g/cm3 and a mass mean diameter between 5 mum and 30 mum, which together yield an aerodynamic diameter of the particles of between approximately one and five microns. The particles may be formed of biodegradable materials such as biodegradable polymers. For example, the particles may be formed of poly(lactic acid) or poly(glycolic acid) or copolymers thereof. Alternatively, the particles may comprise a therapeutic, prophylactic or diagnostic agent and a material selected from the group consisting of surfactant and a molecule having a charge opposite to the charge of the agent and forming a complex thereto. The particles have a tap density less than 0.4 g/cm3 and a mass mean diameter between 5 mum and 30 mum. Exemplary surfactants include phosphoglycerides such as dipalmitoyl phosphatidylcholine (DPPC). The particles are administered to the respiratory tract to permit systemic or local delivery of a wide variety of therapeutic agents. Aggregation of particles before or during administration to the respiratory tract results in particles having an aerodynamic diameter larger than that of the fully dispersed particles. Aerodynamic diameters between three and five microns are advantageous for delivery to the central airways.

3/3/1 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS duplicate ~~patent~~ of patent on page 2A.
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01122616
LARGE POROUS PARTICLES EMITTED FROM AN INHALER
GROSSE POROSE PARTIKELN AUSGESTOSSEN VON EINEM INHALATOR
GRANDES PARTICULES POREUSES EMISES PAR UN INHALATEUR
PATENT ASSIGNEE:
Advanced Inhalation Research, Inc., (2922070), 840 Memorial Drive, Cambridge, MA 02139, (US), (Applicant designated States: all)
INVENTOR:
EDWARDS, David, A. , 171 Commonwealth Avenue Unit 3, Boston, MA 02116,(US)
BATYCKY, Richard, P. , 11 Madison Avenue, Newton, MA 02460, (US)
CAPONETTI, Giovanni, 1137 Massachusetts Avenue 21, Cambridge, MA 02138, (US
LEGAL REPRESENTATIVE:
Kirkham, Nicholas Andrew (83451), Graham Watt & Co., Riverhead, Sevenoaks, Kent TN13 2BN, (GB)
PATENT (CC, No, Kind, Date): EP 1089712 A2 010411 (Basic)
WO 9966903 991229
APPLICATION (CC, No, Date): EP 99930552 990622; WO 99US14074 990622
PRIORITY (CC, No, Date): US 90454 980624
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: A61K-009/12
NOTE: No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English

5/6/2 (Item 2 from file: 349)
00547168
STABLE SPRAY-DRIED PROTEIN FORMULATIONS

5/6/3 (Item 3 from file: 349)
00391829
MATERIALS AND METHODS FOR ENHANCING CELLULAR INTERNALIZATION

5/3,AB/1 (Item 1 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

00780763
LARGE POROUS PARTICLES BY SPRAY-DRYING
FORMULATION PERMETTANT LE SECHAGE PAR ATOMISATION DE GRANDES PARTICULES POREUSES
Patent Applicant/Assignee:
ADVANCED INHALATION RESEARCH INC, 840 Memorial Drive, Cambridge, MA 02139, US, US (Residence), US (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
LIPP Michael M, 1015 Southern Artery, No. 302, Quincy, MA 02169, US, US (Residence), US (Nationality), (Designated only for: US)
BATYCKY Richard P , 11 Madison Avenue, Newton, MA 02460, US, US (Residence), CA (Nationality), (Designated only for: US)
CAPONETTI Giovanni, 807 Somerville Avenue, Somerville, MA 02143, US, US (Residence), IT (Nationality), (Designated only for: US
Legal Representative:
ELMORE Carolyn S (et al) (agent), Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02421, US,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200113892 A2-A3 20010301 (WO 0113892)
Application: WO 2000US23118 20000823 (PCT/WO US0023118)
Priority Application: US 99150662 19990825
Designated States: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
(EP) AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
((OAPI utility model)) BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 11143
English Abstract
Particles having a tap density less than about 0.4 g/cm"sup"3 are formed by spray drying from a colloidal solution including a carboxylic acid or salt thereof, a phospholipid, a divalent salt and a solvent such as an aqueous-organic solvent. The colloidal solution can also include a therapeutic, prophylactic or diagnostic agent. Preferred carboxylic acids include at least two carboxyl groups. Preferred phospholipids include phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phophAtidylserines, phosphatidylinositols and combinations thereof. The particles are suitable for pulmonary delivery.

File 349:PCT FULLTEXT 1983-2001/UB=20011129,UT=20011122
File 350:Derwent WPIX 1963-2001/UD,UM &UP=200170

Set	Items	Description
S1	8	TAP()DENSITY AND BIOACTIVE AND (LUNG OR LUNGS OR PULMONARY)
S2	8	IDPAT (sorted in duplicate/non-duplicate order)
S3	**6**	**IDPAT (primary/non-duplicate records only)**

3/7/1 (Item 1 from file: 350)
DIALOG(R)File 350:Derwent WPIX

013734164
WPI Acc No: 2001-218394/200122
Particles for pulmonary delivery, for modulation of drug release, comprising a bioactive agent and a phospholipid
Patent Assignee: ADVANCED INHALATION RES INC (ADIN-N)
Inventor: BASU S K; CAPONETTI G; DEAVER D R; ELBERT K J; HRKACH J S; LIPP M M; ELBERT K; LI W
Number of Countries: 094 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200113891	A2	20010301	WO 2000US23048	A	20000823	200122	B
AU 200069259	A	20010319	AU 200069259	A	20000823	200136	
US 20010036481	A1	20011101	US 99150742	A	19990825	200168	
			US 2000644736	A	20000823		
			US 2001792869	A	20010223		

Priority Applications (No Type Date): US 99150742 P 19990825; US 2000644736 A 20000823; US 2001792869 A 20010223
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200113891	A2	E	49	A61K-009/16	

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW

AU 200069259	A	A61K-009/16	Based on patent WO 200113891
US 20010036481	A1	A61K-009/14	Provisional application US 99150742 CIP of application US 2000644736

Abstract (Basic): WO 200113891 A2
NOVELTY - Particles for pulmonary delivery comprise a bioactive agent and phospholipid, and have a matrix transition temperature to yield a desired drug release rate.
DETAILED DESCRIPTION - Particles for modulation of drug release comprise:
(a) a bioactive agent; and
(b) a phospholipid or a combination of phospholipids;
where the particles have a matrix transition temperature corresponding to a targeted release rate of the active agent from the particles, and tap density less than 0.4 g/cm3. INDEPENDENT CLAIMS are included for the use of the particles for pulmonary delivery of an active agent, and for increasing the release time of an active agent.
USE - For delivery of therapeutic, prophylactic or diagnostic agents, in humans and animals.
pp; 49 DwgNo 0/7
Derwent Class: B05; B07; C03; C07
International Patent Class (Main): A61K-009/14; A61K-009/16
International Patent Class (Additional): A61K-009/72

3/7/2 (Item 2 from file: 350)
DIALOG(R)File 350:Derwent WPIX

013052674
WPI Acc No: 2000-224529/200019

Production of spray dried particles for delivering active agent to respiratory tract by spraying drying bioactive agent, phospholipid and co-solvent
Patent Assignee: ADVANCED INHALATION RES INC (ADIN-N)
Inventor: EDWARDS D A; HRKACH J S
Number of Countries: 088 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200010541	A1	20000302	WO 99US19306	A	19990825	200019	B
AU 9957842	A	20000314	AU 9957842	A	19990825	200031	
EP 1107743	A1	20010620	EP 99945175	A	19990825	200135	
			WO 99US19306	A	19990825		

Priority Applications (No Type Date): US 9897796 P 19980825
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200010541	A1	E	34	A61K-009/72	

Designated States (National): AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW

AU 9957842	A		A61K-009/72	Based on patent WO 200010541
EP 1107743	A1	E	A61K-009/72	Based on patent WO 200010541

Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

Abstract (Basic): WO 200010541 A1
NOVELTY - Production of spray-dried particles comprises:
(1) combining a bioactive agent, a phospholipid and a co-solvent, the co-solvent including an aqueous solvent and an organic solvent, to form a mixture and
(2) spray-drying the mixture
ACTIVITY - Respiratory.
Human growth hormone was spray-dried in an aqueous/ethanol co-solvent mixture with DPPC. A 70/30 ethanol/aqueous co-solvent (vol/vol) and solute concentrations (combined hGH and DPPC) of 0.1% w/v were used. The pH was 7.4 (NaPO4 buffer). 60/40 hGH/DPPC and 80/20 hGH/DPPC particles were prepared. The tap densities ranged from 0.02 to 0.04 g/cc with mean geometric diameters of 7-8 mum. This gave aerodynamic diameters in the range of 1-3 mum, ideal for inhalation.
USE - The spray-dried particles can be administered to the respiratory tract (claimed) and can be delivered to the pulmonary system.
ADVANTAGE - The spray-dried particles have increased protein stability.
pp; 34 DwgNo 0/0
Derwent Class: B04; B07
International Patent Class (Main): A61K-009/72
International Patent Class (Additional): A61K-009/14

3/3,AB/4 (Item 4 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

00730006
NONAQUEOUS SOLUTIONS AND SUSPENSIONS OF MACROMOLECULES FOR PULMONARY DELIVERY
SOLUTIONS ET SUSPENSIONS NON AQUEUSES DE MACROMOLECULES POUR ADMINISTRATION PAR VOIE PULMONAIRE
Patent Applicant/Assignee:
MASSACHUSETTS INSTITUTE OF TECHNOLOGY, 77 Massachusetts Avenue,

Cambridge, MA 02139, US, US (Residence), US (Nationality)
Inventor(s):
KLIBANOV Alexander M, 45 The Ledges Road, Newton, MA 02459, US
Legal Representative:
PABST Patrea L, Arnall Golden & Gregory, LLP, 2800 One Atlantic Center, 1201 West Peachtree Street, Atlanta, GA 30309-3450, US
Patent and Priority Information (Country, Number, Date):
Patent: WO 200042993 A2 20000727 (WO 0042993)
Application: WO 2000US957 20000114 (PCT/WO US0000957)
Priority Application: US 99116860 19990122; US 99443716 19991119
Designated States: CA JP
(EP) AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
Publication Language: English
Filing Language: English
Fulltext Word Count: 2911
English Abstract
Methods and formulations for delivery of macromolecules, such as proteins, polysaccharides, and nucleic acids, are disclosed, where the macromolecule is dissolved or dispersed in a low toxicity organic solvent which can be aerosolized for delivery to a patient's lungs by inhalation. Optionally, appropriate solubility enhancers are also present in the formulations composition.

3/3,AB/5 (Item 5 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

00485069
STABILIZED BIOACTIVE PREPARATIONS AND METHODS OF USE
PREPARATIONS BIOACTIVES STABILISEES ET LEUR PROCEDES D'UTILISATION
Patent Applicant/Assignee:
ALLIANCE PHARMACEUTICAL CORP,
DELLAMARY Luis A,
TARARA Thomas E,
KABALNOV Alexey,
WEERS Jeffry G,
SCHUTT Ernest G,
Inventor(s):
DELLAMARY Luis A,
TARARA Thomas E,
KABALNOV Alexey,
WEERS Jeffry G,
SCHUTT Ernest G,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9916421 A1 19990408
Application: WO 98US20613 19980929 (PCT/WO US9820613)
Priority Application: US 9760337 19970929; US 98106932 19980629; US 98133848 19980814
Designated States: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 23421
English Abstract
Stabilized dispersions are provided for the delivery of a bioactive

agent. The dispersions preferably comprise a plurality of perforated microstructures dispersed in a suspension medium that typically comprises a liquid fluorochemical. As density variations between the suspended particles and suspension medium are minimized and attractive forces between microstructures are attenuated, the disclosed dispersions are particularly resistant to degradation, such as by settling or flocculation. In particularly preferred embodiments the stabilized dispersions may be directly administered to the lung of a patient using an endotracheal tube or bronchoscope.

3/3,AB/6 (Item 6 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT
(c) 2001 WIPO/Univentio. All rts. reserv.
00485068
STABILIZED PREPARATIONS FOR USE IN NEBULIZERS
PREPARATIONS STABILISEES POUR NEBULISEURS
Patent and Priority Information (Country, Number, Date):
Patent: WO 9916420 A1 19990408
Application: WO 98US20603 19980929 (PCT/WO US9820603)
Priority Application: US 9760337 19970929; US 98106932 19980629; US 98133848 19980814
Designated States: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 25582
English Abstract
Stabilized dispersions are provided for the delivery of a bioactive agent to the respiratory tract of a patient. The dispersions preferably comprise a stabilized colloidal system which may comprise a fluorochemical component. In particularly preferred embodiments, the stabilized dispersions comprises perforated microstructures dispersed in a fluorochemical suspension medium. As density variations between the suspended particles and suspension medium are minimized and attractive forces between microstructures are attenuated, the disclosed dispersions are particularly resistant to degradation, such as by settling or flocculation. In particularly preferred embodiments, the stabilized dispersions may be administered to the lung of a patient using a nebulizer.

File 155:MEDLINE(R) 1966-2001/Dec W4
File 5:Biosis Previews(R) 1969-2001/Nov W4
File 73:EMBASE 1974-2001/Nov W4
File 34:SciSearch(R) Cited Ref Sci 1990-2001/Dec W1
File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec

Set	Items	Description
S1	109	AU="EDWARDS D A"
S2	444	AU="EDWARDS DA"
S3	27	AU="EDWARDS DAVID A"
S4	105	AU="EDWARDS D.A."
S5	32	AU="BATYCKY R":AU="BATYCKY RP"
S6	219	AU="JOHNSTON L"
S7	8	AU="JOHNSTON LLOYD D"
S8	16	AU="JOHNSTON L D"

S9 57 AU="JOHNSTON LD"
S10 0 S1:S4 AND S5 AND S6:S9
S11 1743291 AEROSOL OR TAP()DENSITY OR LUNG OR LUNGS OR PULMONARY
S12 83 S1:S9 AND S11
S13 46 RD (unique items)
S14 7 TAP()DENSITY AND (AEROSOL? OR LUNG OR LUNGS OR PULMONARY)
S15 2 S13 AND S14
S16 44 S13 NOT S15

15/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.
13043210 BIOSIS NO.: 200100250359
Aerodynamically light particles for pulmonary drug delivery.
AUTHOR: Edwards David A (a); Caponetti Giovanni; Hrkach Jeffrey S; Lotan Noah; Hanes Justin; Ben-Jebria Abdell Aziz; Langer Robert S
AUTHOR ADDRESS: (a)State College, PA**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1239 (4):pNo Pagination Oct. 24, 2000
MEDIUM: e-file
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English
ABSTRACT: Improved aerodynamically light particles for drug delivery to the pulmonary system, and methods for their synthesis and administration are provided. In a preferred embodiment, the aerodynamically light particles are made of a biodegradable material and have a tap density less than 0.4 g/cm3 and a mass mean diameter between 5 mum and 30 mum. The particles may be formed of biodegradable materials such as biodegradable polymers. For example, the particles may be formed of a functionalized polyester graft copolymer consisting of a linear alpha-hydroxy-acid polyester backbone having at least one amino acid group incorporated therein and at least one poly(amino acid) side chain extending from an amino acid group in the polyester backbone. In one embodiment, aerodynamically light particles having a large mean diameter, for example greater than 5 mum, can be used for enhanced delivery of a therapeutic agent to the alveolar region of the lung. The aerodynamically light particles incorporating a therapeutic agent may be effectively aerosolized for administration to the respiratory tract to permit systemic or local delivery of wide variety of therapeutic agents.

15/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.
12536903 BIOSIS NO.: 200000290405
Preparation of particles for inhalation.
AUTHOR: Edwards David A (a); Langer Robert S; Vanbever Rit; Mintzes Jeffrey; Wang Jue; Chen Donghao
AUTHOR ADDRESS: (a)State College, PA**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1228 (3):pNo pagination Nov. 16, 1999
MEDIUM: e-file.
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Particles incorporating a surfactant and/or a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a charged molecule of opposite charge for drug delivery to the pulmonary system, and methods for their synthesis and administration are provided. In a preferred embodiment, the particles are made of a biodegradable material and have a tap density less than 0.4 g/cm3 and a mass mean diameter between 5 mum and 30 mum, which together yield an aerodynamic diameter of the particles of between approximately one and three microns. The particles may be formed of biodegradable materials such as biodegradable polymers. For example, the particles may be formed of poly(lactic acid) or poly(glycolic acid) or copolymers thereof. Alternatively, the particles may be formed solely of a therapeutic or diagnostic agent and a surfactant. Surfactants can be incorporated on the particle surface for example by coating the particle after particle formation, or by incorporating the surfactant in the material forming the particle prior to formation of the particle. Exemplary surfactants include phosphoglycerides such as dipalmitoyl phosphatidylcholine (DPPC). The particles can be effectively aerosolized for administration to the respiratory tract to permit systemic or local delivery of wide a variety of therapeutic agents. Formation of complexes of positively or negatively charged therapeutic agents with molecules of opposite charge can allow control of the release rate of the agents into the blood stream following administration.

16/6/4 (Item 4 from file: 155)
10168716 99242271 PMID: 10227712
Large porous particles for sustained protection from carbachol-induced bronchoconstriction in guinea pigs.
Apr 1999

16/6/9 (Item 9 from file: 155)
06021107 88192695 PMID: 3358780
Effect of nitrogen dioxide on surface membrane fluidity and insulin receptor binding of pulmonary endothelial cells.
Apr 15 1988

16/6/10 (Item 10 from file: 155)
05212533 89044829 PMID: 3188015
Vitamin E, membrane order, and antioxidant behavior in lung microsomes and reconstituted lipid vesicles.
Oct 1988

16/6/14 (Item 14 from file: 155)
00160972 99225810 PMID: 10351127
Inhalation of estradiol for sustained systemic delivery.
Spring 1999

16/6/20 (Item 6 from file: 5)
05429430 BIOSIS NO.: 000033030277
CIS VACCENIC ACID INCREASES PLASMA MEMBRANE FLUIDITY AND 5 HYDROXYTRYPTAMINE 5 HT UPTAKE IN PULMONARY ARTERY ENDOTHELIAL CELLS
1987

16/6/21 (Item 7 from file: 5)
05429093 BIOSIS NO.: 000033029940
PARTITIONING OF VITAMIN E AND ITS EFFECT ON LUNG LIPID FLUIDITY AND ANTIOXIDANT BEHAVIOR

1987

16/6/22 (Item 8 from file: 5)
05429088 BIOSIS NO.: 000033029935
ALTERATIONS IN PULMONARY ARTERY ENDOTHELIAL CELL PAEC LIPID COMPOSITION AFFECT SUSCEPTIBILITY TO HYPEROXIC INJURY
1987

16/6/23 (Item 9 from file: 5)
04963723 BIOSIS NO.: 000031038855
EFFECT OF HYPEROXIA AND DIETARY VITAMIN E ON LUNG MITOCHONDRIAL AND MICROSOMAL MEMBRANE FLUIDITY AND LIPID PEROXIDATION
1986

16/6/24 (Item 10 from file: 5)
04963721 BIOSIS NO.: 000031038853
NITROGEN DIOXIDE INCREASES PHOSPHOLIPID CONTENT AND DECREASES SURFACE MEMBRANE FLUIDITY OF PULMONARY ENDOTHELIAL CELLS
1986

16/6/30 (Item 6 from file: 73)
06956307 EMBASE No: 1997240875
Porous dry-powder PLGA microspheres coated with lung surfactant for systemic insulin delivery via the lung
1997

16/6/31 (Item 7 from file: 73)
06744202 EMBASE No: 1997025678
Corrigendum: Aerodynamics and aerosol particle disaggregation phenomena in model oral-pharyngeal cavities (Journal of Aerosol Science (1996) 27(8) (1269-1286))
1997

16/6/35 (Item 1 from file: 34)
09397535 Genuine Article#: 397JH Number of References: 0
Title: Comparative capacitative Ca2+ entry mechanisms in pulmonary and renal arterial smooth muscle cells
Publication date: 20010100

16/6/40 (Item 6 from file: 34)
05489730 Genuine Article#: WC081 Number of References: 1
Title: AERODYNAMICS AND AEROSOL-PARTICLE DISAGGREGATION PHENOMENA IN MODEL ORAL-PHARYNGEAL CAVITIES (VOL 27, PG 1269, 1996)

16/7/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
11716772 21457287 PMID: 11562495
Inhalation delivery of proteins from ethanol suspensions.
Choi WS; Murthy GG; Edwards DA ; Langer R; Klibanov AM
Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA 01239, USA.
Proceedings of the National Academy of Sciences of the United States of America (United States) Sep 25 2001, 98 (20) p11103-7, ISSN 0027-8424
Journal Code: PV3
Contract/Grant No.: GM26698, GM, NIGMS; HD-29125, HD, NICHD
Languages: ENGLISH
Document type: Journal Article

Record type: In Process

To circumvent inherent problems associated with pulmonary administration of aqueous-solution and dry-powder protein drugs, inhalation delivery of proteins from their suspensions in absolute ethanol was explored both in vitro and in vivo. Protein suspensions in ethanol of up to 9% (wt/vol) were readily aerosolized with a commercial compressor nebulizer. Experiments with enzymic proteins revealed that nebulization caused no detectable loss of catalytic activity; furthermore, enzyme suspensions in anhydrous ethanol retained their full catalytic activity for at least 3 weeks at room temperature. With the use of Zn(2+)-insulin, conditions were elaborated that produced submicron protein particles in ethanol suspensions. The latter (insulin/EtOH) afforded respirable-size aerosol particles after nebulization. A 40-min exposure of laboratory rats to 10 mg/ml insulin/EtOH aerosols resulted in a 2-fold drop in the blood glucose level and a marked rise in the serum insulin level. The bioavailability based on estimated deposited lung dose of insulin delivered by inhalation of ethanol suspension aerosols was 33% (relative to an equivalent s.c. injection), i.e., comparable to those observed in rats after inhalation administration of dry powder and aqueous solutions of insulin. Inhalation of ethanol in a relevant amount/time frame resulted in no detectable acute toxic effects on rat lungs or airways, as reflected by the absence of statistically significant inflammatory or allergic responses, damage to the alveolar/capillary barrier, and lysed and/or damaged cells.

Record Date Created: 20010926

16/7/3 (Item 3 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10429164 20036058 PMID: 10571280

Formulation and physical characterization of large porous particles for inhalation.

Vanbever R; Mintzes JD; Wang J; Nice J; Chen D; Batycky R ; Langer R; Edwards DA

Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge 02139, USA.

Pharmaceutical research (UNITED STATES) Nov 1999, 16 (11) p1735-42, ISSN 0724-8741 Journal Code: PHS

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

PURPOSE: Relatively large (>5 microm) and porous (mass density <0.4 g/cm3) particles present advantages for the delivery of drugs to the lungs, e.g., excellent aerosolization properties. **The aim of this study was, first, to formulate such particles with excipients that are either FDA-approved for inhalation or endogenous to the lungs; and second, to compare the aerodynamic size and performance of the particles with theoretical estimates based on bulk powder measurements.** METHODS: Dry powders were made of water-soluble excipients (e.g., lactose, albumin) combined with water-insoluble material (e.g., lung surfactant), using a standard single-step spray-drying process. Aerosolization properties were assessed with a Spinhaler device in vitro in both an Andersen cascade impactor and an Aerosizer. RESULTS: By properly choosing excipient concentration and varying the spray drying parameters, a high degree of control was achieved over the physical properties of the dry powders. Mean geometric diameters ranged between 3 and 15 microm, and tap densities between 0.04 and 0.6 g/cm3. Theoretical estimates of mass mean aerodynamic diameter (MMAD) were rationalized and calculated in terms of geometric particle diameters and bulk tap densities. Experimental values of MMAD obtained from the Aerosizer most closely approximated the theoretical estimates, as compared to those obtained from the Andersen cascade impactor. Particles possessing high porosity

and large size, with theoretical estimates of MMAD between 1-3 microm, exhibited emitted doses as high as 96% and respirable fractions ranging up to 49% or 92%, depending on measurement technique. CONCLUSIONS: Dry powders engineered as large and light particles, and prepared with combinations of GRAS (generally recognized as safe) excipients, may be broadly applicable to inhalation therapy.
Record Date Created: 20000104

16/7/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
09835507 98353477 PMID: 9688708
Recent advances in pulmonary drug delivery using large, porous inhaled particles
Edwards DA ; Ben-Jebria A; Langer R
Department of Chemical Engineering, The Pennsylvania State University, University Park, Pennsylvania 16802, USA.
Journal of applied physiology (UNITED STATES) Aug 1998, 85 (2) p379-85, ISSN 8750-7587 Journal Code: HEG
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed
The ability to deliver proteins and peptides to the systemic circulation by inhalation has contributed to a rise in the number of inhalation therapies under investigation. For most of these therapies, aerosols are designed to comprise small spherical droplets or particles of mass density near 1 g/cm3 and mean geometric diameter between approximately 1 and 3 micron, suitable for particle penetration into the airways or lung periphery. Studies performed primarily with liquid aerosols have shown that these characteristics of inhaled aerosols lead to optimal therapeutic effect, both for local and systemic therapeutic delivery. Inefficient drug delivery can still arise, owing to excessive particle aggregation in an inhaler, deposition in the mouth and throat, and overly rapid particle removal from the lungs by mucocilliary or phagocytic clearance mechanisms. To address these problems, particle surface chemistry and surface roughness are traditionally manipulated. **Recent data indicate that major improvements in aerosol particle performance may also be achieved by lowering particle mass density and increasing particle size, since large, porous particles display less tendency to agglomerate than (conventional) small and nonporous particles. Also, large, porous particles inhaled into the lungs can potentially release therapeutic substances for long periods of time by escaping phagocytic clearance from the lung periphery, thus enabling therapeutic action for periods ranging from hours to many days.** (38 Refs.)
Record Date Created: 19980903

16/7/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
09340456 97334444 PMID: 9188534
Large porous particles for pulmonary drug delivery.
Edwards DA ; Hanes J; Caponetti G; Hrkach J; Ben-Jebria A; Eskew ML; Mintzes J; Deaver D; Lotan N; Langer R
Department of Chemical Engineering, Pennsylvania State University, 204 Fenske Laboratory, University Park, PA 16802, USA. dxe11@psuv.edu
Science (UNITED STATES) Jun 20 1997, 276 (5320) p1868-71, ISSN 0036-8075 Journal Code: UJ7
Contract/Grant No.: GM26698, GM, NIGMS; HD29125, HD, NICHD
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

A new type of inhalation aerosol , characterized by particles of small mass density and large size, permitted the highly efficient delivery of inhaled therapeutics into the systemic circulation. **Particles with mass densities less than 0.4 gram per cubic centimeter** and mean diameters exceeding 5 micrometers were inspired deep into the lungs and escaped the lungs' natural clearance mechanisms until the inhaled particles delivered their therapeutic payload. Inhalation of large porous insulin particles resulted in elevated systemic levels of insulin and suppressed systemic glucose levels for 96 hours, whereas small nonporous insulin particles had this effect for only 4 hours. High systemic bioavailability of testosterone was also achieved by inhalation delivery of porous particles with a mean diameter (20 micrometers) approximately 10 times that of conventional inhaled therapeutic particles.
Record Date Created: 19970701

16/7/15 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.
13157078 BIOSIS NO.: 200100364227
Porous particles for deep lung delivery.
AUTHOR: Edwards David A (a); Caponetti Giovanni; Hrkach Jeffrey S; Lotan Noah; Hanes Justin; Langer Robert S; Ben-Jebria Abdellaziz
AUTHOR ADDRESS: (a)Boston, MA**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1248 (1):pNo Pagination July 3, 2001
MEDIUM: e-file
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English
ABSTRACT: **Improved porous particles for drug delivery to the pulmonary system, and methods for their synthesis and administration are provided.** In a preferred embodiment, the porous particles are made of a biodegradable material and **have a mass density less than 0.4 g/cm3 /.** The particles may be formed of biodegradable materials such as biodegradable polymers. For example, the particles may be formed of a functionalized polyester graft copolymer consisting of a linear alpha-hydroxy-acid polyester backbone having at least one amino acid group incorporated therein and at least one poly(amino acid) side chain extending from an amino acid group in the polyester backbone. In one embodiment, porous particles having a relatively large mean diameter, for example greater than 5 mum, can be used for enhanced delivery of a therapeutic agent to the alveolar region of the lung . The porous particles incorporating a therapeutic agent may be effectively aerosolized for administration to the respiratory tract to permit systemic or local delivery of wide variety of therapeutic agents.

16/7/16 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.
12538537 BIOSIS NO.: 200000292039
Materials and methods for enhancing cellular internalization.
AUTHOR: Edwards David A (a); Deaver Daniel R; Langer Robert S
AUTHOR ADDRESS: (a)Newton, MA**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1228 (3):pNo pagination Nov. 16, 1999
MEDIUM: e-file.

ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English
ABSTRACT: **Compositions and methods for delivering agents across cell membranes are disclosed.** The compositions include an agent to be delivered, a viscous material, such as a hydrogel, lipogel or viscous sol, and, optionally, a carrier that includes a ligand that binds to or interacts with cell surface receptors. The agent to be delivered binds to or otherwise interacts with cell surface receptors, is attached, either covalently or ionically to a molecule that binds to or interacts with a cell surface receptor, or is associated with the carrier. Agents to be delivered include bioactive compounds and diagnostic agents. The compositions have an apparent viscosity roughly equal to the viscosity of the cytosol in the cell to which the agent is to be delivered. The rate of cellular internalization is higher when the viscosity of the viscous material and that of the cytosol in the cell are approximately the same, relative to when they are not the same. The compositions enhance cellular entry of bioactive agents and diagnostic materials when administered vaginally, nasally, rectally ocularly, orally, or to the respiratory or pulmonary system.

16/7/17 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12408803 BIOSIS NO.: 200000162305
Sustained release of insulin from insoluble inhaled particles.
AUTHOR: Vanbever Rita(a); Ben-Jebria Abdellaziz; Mintzes Jeffrey D; Langer Robert; Edwards David A
AUTHOR ADDRESS: (a)Department of Pharmaceutical Technology, School of Pharmacy, Universite Catholique de Louvain, Avenue E. Mounier, UCL 73.20, 1200, Brussels**Belgium
JOURNAL: Drug Development Research. 48 (4):p178-185 Dec., 1999
ISSN: 0272-4391
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT: Conventional slow-acting insulin preparations for subcutaneous injection, e.g., suspensions of the complex with protamine and/or zinc, were reformulated as dry powders for inhalation and the insoluble aerosol tested for providing sustained insulin plasma levels. Large porous particles made of lactose, albumin, and dipalmitoylphosphatidylcholine, and incorporating insulin, protamine, and/or zinc chloride were prepared using spray-drying. Integrity of insulin after spray-drying and insulin insolubilization in spray-dried particles was verified in vitro. The pharmacokinetic profile of the formulation delivered by inhalation and subcutaneous injection was assessed in vivo in the rat. The formulation process on insulin as dry powders did not alter insulin integrity and did not impede, in most cases, insulin insolubilization by protamine and/or zinc. Large porous insulin particles presented 7 mum mass mean geometric particle diameters, **0.1 g/cm3 bulk powder tap densities** and theoretical aerodynamic diameters suitable for deep lung deposition (in the range of 2.2-2.5 mum). The **dry powders exhibited 40% respirable fractions in the Andersen cascade impactor and 58-75% in the Aero-BreatherTM.** Insoluble inhaled insulin provided sustained insulin plasma levels for half a day, similar to injected insulin, and exhibited a bioavailability of 80.5% relative to subcutaneous injection of the same formulation.

16/7/18 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.
11826956 BIOSIS NO.: 199900073065
Particles incorporating surfactants for pulmonary drug delivery.
AUTHOR: Hanes J; Edwards D A ; Evora C; Langer R
AUTHOR ADDRESS: Baltimore, Md.**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1218 (1):p303-304 Jan. 5, 1999
ISSN: 0098-1133
RECORD TYPE: Citation
LANGUAGE: English

16/7/19 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.
11046519 BIOSIS NO.: 199799667664
Aerosol particle transport and deaggregation phenomena in the mouth and throat.
AUTHOR: Li Wen-I; Edwards David A (a
AUTHOR ADDRESS: (a)Dep. Chem. Engineering, Penn State Univ., University Park, PA 16802**USA
JOURNAL: Advanced Drug Delivery Reviews 26 (1):p41-49 1997
ISSN: 0169-409X
DOCUMENT TYPE: Literature Review
RECORD TYPE: Citation
LANGUAGE: English

16/7/25 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.
11339143 EMBASE No: 2001352532
Inhalation delivery of proteins from ethanol suspensions
Won Seon Choi; Murthy G.G.K.; Edwards D.A. ; Langer R.; Klibanov A.M.
A.M. Klibanov, Department of Chemistry, Massachusetts Institute of Tech., Cambridge, MA 02139 United States
AUTHOR EMAIL: klibanov@mit.edu
Proceedings of the National Academy of Sciences of the United States of America (PROC. NATL. ACAD. SCI. U. S. A.) (United States) 25 SEP 2001 , 98/20 (11103-11107)
CODEN: PNASA ISSN: 0027-8424
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 48
To circumvent inherent problems associated with pulmonary administration of aqueous-solution and dry-powder protein drugs, inhalation delivery of proteins from their suspensions in absolute ethanol was explored both in vitro and in vivo. Protein suspensions in ethanol of up to 9% (wt/vol) were readily aerosolized with a commercial compressor nebulizer. Experiments with enzymic proteins revealed that nebulization caused no detectable loss of catalytic activity; furthermore, enzyme suspensions in anhydrous ethanol retained their full catalytic activity for at least 3 weeks at room temperature. With the use of ZnSUP2+-insulin, conditions were elaborated that produced submicron protein particles in ethanol suspensions. The latter (insulin/EtOH) afforded respirable-size aerosol particles after nebulization. A 40-min exposure of laboratory rats to 10 mg/ml insulin/EtOH aerosols resulted in a 2-fold drop in the blood

glucose level and a marked rise in the serum insulin level. The bioavailability based on estimated deposited lung dose of insulin delivered by inhalation of ethanol suspension aerosols was 33% (relative to an equivalent s.c. injection), i.e., comparable to those observed in rats after inhalation administration of dry powder and aqueous solutions of insulin. Inhalation of ethanol in a relevant amount/time resulted in no detectable acute toxic effects on rat lungs or airways, as reflected by the absence of statistically significant inflammatory or allergic responses, damage to the alveolar/capillary barrier, and lysed and/or damaged cells.

16/7/26 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.
11011160 EMBASE No: 2001045342
Physical characterization of large porous particles for inhalation (multiple letters)
Gupta R.; Byron P.R.; Vanbever R.; Mintzes J.; Nice J.; Chen D.; Batycky R. ; Langer R.; Edwards D.A.
R. Gupta, Aerosol Research Group, School of Pharmacy, Virginia Commonwealth University/MCV, Richmond, VA United States
Pharmaceutical Research (PHARM. RES.) (United States) 2000, 17/11 (1437-1438)
CODEN: PHREE ISSN: 0724-8741
DOCUMENT TYPE: Journal ; Letter
LANGUAGE: ENGLISH

16/7/27 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.
10959709 EMBASE No: 2001004643
Inhalation system for pulmonary aerosol drug delivery in rodents using large porous particles
Ben-Jebria A.; Eskew M.L.; Edwards D.A.
A. Ben-Jebria, Department of Chemical Engineering, Environ. Resources Res. Institute, Pennsylvania State University, University Park, PA 16802 United States
Aerosol Science and Technology (AEROSOL SCI. TECHNOL.) (United States) 2000, 32/5 (421-433)
CODEN: ASTYD ISSN: 0278-6826
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 17
The pulmonary system is an attractive noninvasive route for effective delivery of drugs for both local and systemic therapies. In this study, an inhalation system was developed to effectively aerosolize and deliver small amounts (typically 1-5 mg) of dry powder polymeric and nonpolymeric particles to the lungs of anesthetized rodents over a very short period of time using a ventilator while the animals breathed spontaneously. The **new aerosols were designed for size, porosity, and lightness and were characterized by particles of low mass density (p <= 0.1 g/cmSUP3) and large size (d ~ 10 mum)**. The inhalation system was tested in vivo to determine 1) whether the relatively efficient in vitro aerosolization of these large porous particles translated into a substantial respirable fraction in vivo; 2) whether the bioavailability of an encapsulated drug for systemic therapy could be increased and the drug release in the systemic circulation could be sustained; and 3) whether an encapsulated

drug for local asthma therapy could sustain bronchodilation over a prolonged time period. Unlike the conventional (small nonporous) particles which deposit primarily in the tubing and trachea (80% of all particle mass delivered), 55% of the large porous particle mass deposited in the deep lung . The total systemic bioavailabilities of inhaled porous estradiol, insulin, and testosterone relative to subcutaneous injections were 86%, 88%, and 177%, respectively. The inhaled dry powder albuterol sulfate aerosol was capable of preventing sustained bronchoconstriction (in response to carbachol challenge) for approximately one day. Our data indicate that the experimental inhalation system we developed will be an excellent device for further testing of new therapeutics available in particulate form.

16/7/28 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

07363441 EMBASE No: 1998270091
The macrotransport properties of aerosol particles in the human oral-pharyngeal region
Li W.-I.; Perzl M.; Ferron G.A.; Batycky R. ; Heyder J.; Edwards D.A.
D.A. Edwards, 204 Fenske Laboratory, Penn State University, University Park, PA 16802 United States
Journal of Aerosol Science (J. AEROSOL SCI.) (United Kingdom) 1998, 29/8 (995-1010)
CODEN: JALSB ISSN: 0021-8502
PUBLISHER ITEM IDENTIFIER: S0021850297100404
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 32
A method is described for evaluating the mean velocity, dispersion coefficient and deposition rate constant characterizing aerosol transport in a finite, computationally tractable, three-dimensional domain of the human lungs . The methodology is applied specifically to deduce (mesoscale) transport coefficients in an anatomically realistic human mouth and throat. In this method aerosol particles are introduced into a numerically simulated airflow in the vicinity of the entrance region of the airway unit (e.g. the mouth); the aerosol bolus is inspired such that it travels through the airway unit before being expired. The exhaled concentration of nondeposited aerosols is determined numerically, and used to deduce the three aerosol transport coefficients. The deduced transport coefficients, representing 'mesoscale' averages of the microscale simulated flow, are determined as functions of air flow rate, particle size, bolus parameters, and dimensionality; these values are then incorporated into a mesoscale lung model and used to simulate macroscale aerosol transport behavior in the lungs . Special attention is given to the numerical simulation of an aerosol bolus inspired into the lungs . The calculated half-width, mode and deposition fraction agree favorably with recent macrotransport simulations, minus the upper airway generation. In these comparisons, the major influence of the upper airways is to increase aerosol deposition. Half-width and deposition fraction are also significantly affected by lung size.

16/7/29 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

06956312 EMBASE No: 1997240880
Large porous aerosols for pulmonary drug delivery

Edwards D.A. ; Caponetti G.; Hrkach J.; Hanes J.; Lotan N.; Ben-Jebria A.; Langer R.
D.A. Edwards, Department of Chemical Engineering, Pennsylvania State University, University Park, PA 16802 United States
Proceedings of the Controlled Release Society (PROC. CONTROL. RELEASE SOC.) (United States) 1997, -/24 (67-68)
CODEN: 58GMA ISSN: 1022-0178
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 6

16/7/33 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.
06670662 EMBASE No: 1996335566
Numerical simulation of air and particle transport in the conducting airways
Ferron G.A.; Edwards D.A.
GSF Research Centre for Environment, Hlth. Inst. for Inhalation Biology, PO Box 1129,D85758 Oberschleissheim Germany
Journal of Aerosol Medicine: Deposition, Clearance, and Effects in the Lung (J. AEROSOL. MED. DEPOSITION CLEAR. EFF. LUNG) (United States) 1996, 9/3 (3Q3-316)
CODEN: JAEME ISSN: 0894-2684
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
The results of numerical simulations of air and particle transport through symmetrically branching airways are summarized. These results shed light upon differences in simulated flow and particle transport behavior for (1) steady versus unsteady flow patterns, (2) two- versus three-dimensional geometries, and (3) natural versus forced user-defined entrance and exit boundary conditions. It is shown that the 'steady-flow' approximation of inherently unsteady airway transport can lead to a loss of resolution of unique airflow patterns that appear to arise during the process of flow reversal. Assuming a two-dimensional geometry can result in a substantial underprediction of aerodynamic stresses, especially in the case of turbulent flows. Also, assigning entrance and exit boundary conditions can lead to the observation of gas and aerosol transport effects that do not occur during the course of natural breathing processes. It is shown that these latter effects may potentially be eliminated by extending the spatial domain under consideration, permitting identification of intrinsic airway transport properties that can be used for the study of lung transport phenomena in a macrotransport lung model. Two potential applications are discussed: (1) the use of numerical simulations to understand the role of airway morphology in the alteration of aerosol transport in diseased (versus healthy) lungs , and (2) the use of simulations for the design of aerosol particles for targeted drug delivery to the lung .

16/7/36 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.
08153398 Genuine Article#: 230DT Number of References: 0
Title: Inhalation system for pulmonary drug delivery in rodents.
Author(s): BenJebria A; Edwards DA
Corporate Source: PENN STATE UNIV,DEPT CHEM ENGN/UNIVERSITY PK//PA/16802; ADV INHALAT RES,/CAMBRIDGE//MA/02139
Journal: AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, 1999

, V159, N3,S (MAR), PA119-A119
ISSN: 1073-449X Publication date: 19990300
Publisher: AMER LUNG ASSOC, 1740 BROADWAY, NEW YORK, NY 10019
Language: English Document Type: MEETING ABSTRACT

16/7/38 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.
07522927 Genuine Article#: 176JP Number of References: 0
Protein delivery to the lungs with large porous particle dry powders.
Author(s): Edwards DA ; Hrkach J; Schmitke J; Berkovitz D; Yancey D; Niven R
Corporate Source: ADV INHALAT RES INC,/CAMBRIDGE//MA/02139
Journal: ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, 1999, V217, 2 (MAR 21), P194-POLY
ISSN: 0065-7727 Publication date: 19990321
Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036
Language: English Document Type: MEETING ABSTRACT

16/7/39 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.
06515240 Genuine Article#: YY474 Number of References: 19
Title: Microscopic and macroscopic descriptions of gas and aerosol transport in the human lung
Author(s): Batycky RP ; Edwards DA (REPRINT)
Corporate Source: PENN STATE UNIV,DEPT CHEM ENGN, 204 FENSKE LAB/UNIVERSITY PK//PA/16802 (REPRINT); PENN STATE UNIV,DEPT CHEM ENGN/UNIVERSITY PK//PA/16802; MIT,DEPT CHEM ENGN/CAMBRIDGE//MA/02139
Journal: CHEMICAL ENGINEERING COMMUNICATIONS, 1996, V150, P23-39
ISSN: 0098-6445 Publication date: 19960000
Publisher: GORDON BREACH SCI PUBL LTD, C/O STBS LTD, PO BOX 90, READING, BERKS, ENGLAND RG1 8JL
Language: English Document Type: ARTICLE
Abstract: **This article discusses the validity of describing single-breath, gas or aerosol bolus transport processes** in terms of effective Gaussian characteristics. This is done in the context of a comparison between the predictions of a recent macrotransport model of pulmonary transport phenomena and predictions based upon the numerical solution of a so-called 'exact' microtransport problem. In addition, comparison is made with the predictions of a former network model of convective dispersion in the conducting airways of the lung . For conditions of physiological interest, the macrotransport model is shown to predict to within reasonable accuracy the mode (i.e., time of exit of the peak of an inspired bolus) as well as the dispersion of gas or aerosol for the case of an impulsive introduction of the gas/aerosol bolus (varying the shape and size of the bolus). The relative merits of micro-and macroscopic descriptions of lung transport problems are discussed. Comparisons with experimental data, as well as a discussion of the implications of the present study on the future development of transport models of lung dispersion, are provided.

16/7/41 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.
03842360 Genuine Article#: QK935 Number of References: 33
Title: THE MACROTRANSPORT OF AEROSOL-PARTICLES IN THE LUNG - AEROSOL DEPOSITION PHENOMENA

Author(s): EDWARDS DA
Corporate Source: MIT,DEPT CHEM ENGN/CAMBRIDGE//MA/02139
Journal: JOURNAL OF AEROSOL SCIENCE, 1995, V26, N2 (MAR), P293-317
ISSN: 0021-8502
Language: ENGLISH Document Type: ARTICLE
Abstract: The macrotransport model of lung dispersion (Edwards, 1994) is generalized to incorporate phenomena involving the nonconservation of gas and/or aerosol species in the airways and acini of the human lung during a single breath. The three principal parameters measured in **single-breath gas or aerosol bolus dispersion experiments**, namely, net deposition rate ((K) over bar*), mean bolus velocity ((U) over bar*) and effective dispersion coefficient (D) over bar*), are theoretically determined in terms of the detailed microtransport, branch-level phenomena underlying them. Explicit formulas are provided for the macroscale coefficients ((K) over bar*, (U) over bar*, (D) over bar*). Additionally, a formula is provided for a coefficient (A) over bar* that serves to characterize a novel ''apparent initial condition'' to be imposed upon the aerosol concentration profile as viewed from its coarse-grained level.

Numerical calculations are made in the case of aerosols. These are based upon a symmetrical Weibel model A geometry, and employ the deposition model of Landahl (1950) for assigning constitutive laws to the branch-level deposition-rate parameters that underly the theory. Branch-level dispersion coefficients are described by an axial-streaming constitutive law, as in the previous contribution, while taking explicit account of the diminution of axial streaming caused by aerosol deposition. Comparison is made with the aerosol bolus experimental data of Heyder et al. (1988) and Anderson rt al. (1989). Predictions of net aerosol deposition in the human lung as a function of aerosol particle size are compared with predictions made on the basis of former aerosol -deposition theories, as well as with additional aerosol -deposition data appearing in the literature. Very good agreement is found for all of these comparisons.

16/7/42 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03250031 Genuine Article#: NQ279 Number of References: 58
Title: A GENERAL-THEORY OF THE MACROTRANSPORT OF NONDEPOSITING PARTICLES IN THE LUNG BY CONVECTIVE DISPERSION
Author(s): EDWARDS DA
Corporate Source: MIT,DEPT CHEM ENGN/CAMBRIDGE//MA/02139
Journal: JOURNAL OF AEROSOL SCIENCE, 1994, V25, N3 (APR), P543-565
ISSN: 0021-8502
Language: ENGLISH Document Type: ARTICLE
Abstract: A theoretical model of (gas or) aerosol -particle dispersion phenomena in the conducting airways and acini of a symmetrically-bifurcating lung network is proposed. Founded upon the methods of macrotransport analysis for spatially periodic systems (Brenner and Edwards, Macro-transport Processes, Butterworth-Heinemann, Boston, 1993), the model characterizes the transport of nondepositing aerosol particles (or gas molecules) into and out of the lung (following a single inhalation/exhalation breath cycle) as occurring within a spatially periodic expanding/contracting branched network of one-dimensional capillaries (whose transport properties depend, inter alia, upon their specific cross-sectional geometrical and physicochemical characteristics). The model is shown to generalize and

(in this and a subsequent article) improve upon former network models of lung dispersion. General formulas are derived for the mean velocity U*BAR with which an aerosol bolus transports through the network (at constant gas flow rate), as well as for the dispersion D*BAR about this mean. Various physical bases of the model in regards to dispersion phenomena in the lung are discussed, as is the experimental accessibility of the effective transport coefficients U*BAR and D*BAR. Explicit expressions for U*BAR and D*BAR are derived in various limits. These are compared with numerical results based upon the symmetrical Weible Model A of the human lung in the special cases of (i) Taylor dispersion within the airways, for which comparison is made with former network models; and (ii) axial streaming within the airways, for which comparison is made with experimental data. In the latter case, encouraging agreement is found between theory and experiments when the degree of axial streaming in the conducting airways is chosen to be similar as that observed in the branched-tube-network experiments of Scherer et al.

16/7/43 (Item 9 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02323195 Genuine Article#: KU148 Number of References: 29
Title: DISPERSION AND REACTION IN 2-DIMENSIONAL MODEL POROUS-MEDIA
Author(s): EDWARDS DA ; SHAPIRO M; BRENNER H
Corporate Source: MIT,DEPT CHEM ENGN/CAMBRIDGE//MA/02139; TECHNION ISRAEL INST TECHNOL,FAC MECH ENGN/IL-32000 HAIFA//ISRAEL/
Journal: PHYSICS OF FLUIDS A-FLUID DYNAMICS, 1993, V5, N4 (APR), P837-848
ISSN: 0899-8213
Language: ENGLISH Document Type: ARTICLE
Abstract: Darcy-scale convective-diffusive-reactive phenomenological coefficients characterizing the transport of a reactive solute through the interstices of a two-dimensional, spatially periodic, model porous medium (on whose surfaces the solute undergoes a first-order, irreversible chemical reaction) are herein determined numerically as functions of the microscale Peclet (Pe), Damkohler (Da), and Reynolds (Re) numbers. The role of bed porosity E and (circular) cylindrical array configuration are also studied, the latter encompassing square, staggered, and hexagonal arrays. Calculations are effected via generalized Taylor dispersion theory. The Darcy-scale reactivity coefficient K*BAR characterizing the effective (first-order, irreversible) volumetric reaction rate is found, inter alia, to be (approximately) inversely proportional to Pe, a conclusion confirmed by analytical results for the limiting case of small Da. Configurational properties of the porous medium are observed to significantly influence K*BAR, especially for small porosities and large Da. Moreover, it is found that the mean interstitial velocity vector U*BAR of the reactive solute generally differs (often dramatically) from the comparable velocity vector (1/epsilon)U*BAR of the (inert) solvent as a consequence of the chemical reaction occurring at the surfaces of the cylindrical bed particles. These data reveal that the mean solute speed \U*BAR\ through the interstices may be larger or smaller than the comparable solvent speed (1/epsilon)\UBAR\, depending upon the existence and nature of a diffusive boundary layer adhering to the cylindrical bed-particle surfaces. Finally, the longitudinal and lateral components of the solute's (transversely isotropic) dispersivity dyadic D*BAR, parallel and perpendicular, respectively, to the direction of mean flow, are generally observed to decrease with

increasing Da. This behavior stems from the fact that, in the diffusion boundary-layer limit, an increasing proportion of the total depletion of solute (via microscale reaction at the cylinder surfaces) arises from those interstitial zones characterized by the existence of large velocity gradients.

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File 155:MEDLINE(R) 1966-2001/Dec W5
File  73:EMBASE 1974-2001/Nov W4
File 144:Pascal 1973-2001/Dec W1
File  35:Dissertation Abs Online 1861-2001/Nov
File  42:Pharmaceuticl News Idx 1974-2001/Nov W3
File 162:CAB HEALTH 1983-2001/Oct
File   8:Ei Compendex(R) 1970-2001/Dec W1
File   2:INSPEC 1969-2001/Dec W1
File   5:Biosis Previews(R) 1969-2001/Nov W4
File   6:NTIS 1964-2001/Dec W3
File  34:SciSearch(R) Cited Ref Sci 1990-2001/Dec W1
File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
File  65:Inside Conferences 1993-2001/Dec W1
File  77:Conference Papers Index 1973-2001/Nov
File  94:JICST-EPlus 1985-2001/Oct W4
File  99:Wilson Appl. Sci & Tech Abs 1983-2001/Sep
File  50:CAB Abstracts 1972-2001/Oct
File 315:ChemEng & Biotec Abs 1970-2001/Oct
File  74:Int.Pharm.Abs. 1970-2001/Oct
File  71:ELSEVIER BIOBASE 1994-2001/Dec W1
File 285:BioBusiness(R) 1985-1998/Aug W1
File  76:Life Sciences Collection 1982-2001/Nov
File  19:Chem.Industry Notes 1974-2001/ISS 200148
File 446:IMSWorld Product Launches 1982-2001/Nov
File 305:Analytical Abstracts 1980-2001/Dec W1
Set     Items   Description
S1     497036   INHAL????? OR AEROSOL? ?
S2    2414013   PARTICLE? ? OR MIST OR POWDER??
S3        376   TAP()(DENSITY OR DENSITIES)
S4     169788   BIOACTIVE
S5     220483   RECEPTACLE? ? OR CONTAINER? ? OR NEBULI?ER? ? OR ATOMI?ER?
              ? OR VAPORI?ER? ?
S6    2886302   DENSITY OR DENSITIES
S7     901413   TAP??? OR VIBRAT????
S8        341   S2(5N)(S3 OR S6(2N)S7)
S9        381   S2(5N)S4
S10   1759292   VOLUME
S11      2004   S5(3N)S10
S12         0   S8 AND S9 AND S11
S13         0   S8 AND S9
S14         0   S8 AND S11
S15       350   S2 AND S3
S16     13241   S10 AND S5
S17         0   S11 AND S15
S18       378   S1 AND S11
S19        19   S1 AND S15
S20         6   RD (unique items)
S21    108963   CM3 OR CC OR CU()CM OR CUBIC()CENTIMETER? ?
S22         4   S18 AND S21
S23         3   RD (unique items)
```

20/6,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:
11303667 21111976 PMID: 11182203
Influence of formulation excipients and physical characteristics of inhalation dry powders on their aerosolization performance.
Feb 23 2001
... of **this study was to determine the effects of formulation excipients and physical characteristics of inhalation particles on their in vitro aerosolization performance, and thereby to maximize their respirable fraction.** Dry powders were produced by spray-drying using excipients that are FDA-approved for inhalation as lactose, materials that are endogenous to the lungs as albumin and dipalmitoylphosphatidylcholine (DPPC); and/or protein stabilizers as trehalose or mannitol. Dry powders suitable for deep lung deposition, i.e. with an aerodynamic diameter of individual particles <3 microm, were prepared. They presented 0.04--0.25 g/cm(3) bulktap densities , 3--5 microm geometric particle sizes, up to 90% emitted doses and 50% respirable fractions in the Andersen cascade impactor using a Spinhaler inhaler device. The incorporation of lactose, albumin and DPPC in the formulation all improved the aerosolization properties, in contrast to trehalose and the mannitol which decreased powder flowability. The relative proportion of the excipients affected aerosol performance as well. The lower the bulk powder tap density, the higher the respirable fraction. Optimization of in vitro aerosolization properties of inhalation dry powders can be achieved by appropriately selecting composition and physical characteristics of the particles .

23/6/1 (Item 1 from file: 73)
DIALOG(R)File 73:(c) 2001 Elsevier Science B.V. All rts. reserv.
00751901 EMBASE No: 1977097281
A simple method for quantitative inhalation test with allergens
1976

23/6/2 (Item 1 from file: 144)
DIALOG(R)File 144:(c) 2001 INIST/CNRS. All rts. reserv.
11106958 PASCAL No.: 93-0613981
Particle size measurement in the submicron range by the differential electromobility technique : comparision of aerosols from thermospray, ultrasonic, pneumatic and frit-type nebulizers
1993

File 319:Chem Bus NewsBase 1984-2001/Dec 04
File 143:Biol. & Agric. Index 1983-2001/Sep

Set	Items	Description
S1	4323	INHAL????? OR AEROSOL? ?
S2	18117	PARTICLE? ? OR MIST OR POWDER??
S3	1	TAP()(DENSITY OR DENSITIES)
S4	496	BIOACTIVE
S5	5971	RECEPTACLE? ? OR CONTAINER? ? OR NEBULI?ER? ? OR ATOMI?ER? ? OR VAPORI?ER? ?
S6	20412	DENSITY OR DENSITIES
S7	4278	TAP??? OR VIBRAT????
S8	0	S1 AND (S3 OR S6(2N)S7)
S9	4	S2 AND (S3 OR S6(2N)S7)
S10	9	S1 AND S5 AND VOLUME
S11	13	S9 OR S10

S12 13 RD (unique items) [not relevant]

File 16:Gale Group PROMT(R) 1990-2001/Dec 03
File 160:Gale Group PROMT(R) 1972-1989
File 96:FLUIDEX 1972-2001/Nov
File 148:Gale Group Trade & Industry DB 1976-2001/Dec 03
File 9:Business & Industry(R) Jul/1994-2001/Dec 03
File 98:General Sci Abs/Full-Text 1984-2001/Oct
File 174:Pharm-line(R) 1978-2001/Nov W2
File 88:Gale Group Business A.R.T.S. 1976-2001/Dec 04
File 636:Gale Group Newsletter DB(TM) 1987-2001/Dec 03
File 484:Periodical Abs Plustext 1986-2001/Dec W1
File 149:TGG Health&Wellness DB(SM) 1976-2001/Nov W3
File 551:TFSD Worldwide M&A 1980-2001/Dec 04
File 621:Gale Group New Prod.Annou.(R) 1985-2001/Dec 03
File 813:PR Newswire 1987-1999/Apr 30
File 20:World Reporter 1997-2001/Dec 04

Set	Items	Description
S1	118727	INHAL????? OR AEROSOL? ?
S2	462195	PARTICLE? ? OR MIST OR POWDER??
S3	33	TAP()(DENSITY OR DENSITIES)
S4	5843	BIOACTIVE
S5	482048	RECEPTACLE? ? OR CONTAINER? ? OR NEBULI?ER? ? OR ATOMI?ER? ? OR VAPORI?ER? ?
S6	413850	DENSITY OR DENSITIES
S7	1317638	TAP??? OR VIBRAT????
S8	0	S1(S)S2(5N)(S3 OR S6(2N)S7)
S9	42	S1 AND S2 AND (S3 OR S6(S)S7)
S10	3	S1 AND S3
S11	**2**	**RD (unique items)**
S12	2086679	VOLUME
S13	119743	CM3 OR CC OR CU()CM OR CUBIC()CENTIMET???
S14	48	S1 AND S5(S)(S12 AND S13)
S15	0	S9 AND S14
S16	48	S14
S17	32	RD (unique items)
S18	2	S17/2001
S19	3009558	PD=20000901:20001231
S20	**29**	**S17 NOT S18:S19**
S21	42	S9
S22	5	S21/2001
S23	37	S21 NOT (S22 OR S19)
S24	**28**	**RD (unique items)**

11/3,AB/1 (Item 1 from file: 148)
DIALOG(R)File 148:Gale Group Trade & Industry DB
(c)2001 The Gale Group. All rts. reserv.
09329217 SUPPLIER NUMBER: 19075724 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Particulate Materials Center researches powder processing.
Sheppard, Laurel M.
Ceramic Industry, v146, n12, p35(4)
Nov, 1996
ISSN: 0009-0220 LANGUAGE: English RECORD TYPE: Fulltext
WORD COUNT: 1773 LINE COUNT: 00155

20/6/13 (Item 10 from file: 148)

03938436 SUPPLIER NUMBER: 08263515 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Tips on technology. (blood bank, chemistry, hematology, immunology, microbiology)(Clinical Laboratory Reference 1989)
Annual, 1989
WORD COUNT: 15692 LINE COUNT: 01252

20/6/14 (Item 11 from file: 148)
03938434 SUPPLIER NUMBER: 08263509 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Product information section. (Clinical Laboratory Reference 1989) (buyers guide)
Annual, 1989
WORD COUNT: 64583 LINE COUNT: 05915

20/6/16 (Item 1 from file: 636)
03920841 Supplier Number: 50150196 (USE FORMAT 7 FOR FULLTEXT)
FEDERAL REGISTER
July 6, 1998
Word Count: 6249

20/6/25 (Item 8 from file: 149)
01377423 SUPPLIER NUMBER: 12407472 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Lung function and bronchial responsiveness after bronchoalveolar lavage and bronchial biopsy performed without premedication in stable asthmatic subjects.
1992
WORD COUNT: 3262 LINE COUNT: 00360

20/3,AB,K/4 (Item 1 from file: 148)
DIALOG(R)File 148:Gale Group Trade & Industry DB
(c)2001 The Gale Group. All rts. reserv.
12363532 SUPPLIER NUMBER: 62766813 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Quick Albuterol Nebulizer Cuts ER Time, Costs.
ZOLER, MITCHEL L.
Family Practice News, 30, 8, 54
April 15, 2000
ISSN: 0300-7073 LANGUAGE: English RECORD TYPE: Fulltext
WORD COUNT: 573 LINE COUNT: 00048
TEXT:
NEW ORLEANS -- A new nebulizer that cuts the time for administering inhaled albuterol for acute asthma was as safe and effective as a conventional nebulizer in a...
... from reaching the patient's mouth. Larger droplets deposit in the mouth instead of being inhaled , and then go down the throat and are absorbed systemically. Because this is prevented with...
... Forty-nine patients were randomized to treatment with a conventional, Hudson nebulizer . They received a standard dose of 0.09 cc albuterol/kg, which was diluted with saline to a total volume of 12 cc . The nebulizer flow rate was set to 8 L/min; it took 45 minutes to deliver the medication.
Fifty-five patients were randomized to the Circulaire group. They received 2 cc of undiluted albuterol during the first treatment and 1 cc during subsequent treatments, when needed, with a maximum of three treatments per episode. With a nebulizer flow rate of 8 L/min, the dose was delivered in 4 minutes...

20/3,AB/8 (Item 5 from file: 148)
DIALOG(R)File 148:Gale Group Trade & Industry DB
(c)2001 The Gale Group. All rts. reserv.
06764472 SUPPLIER NUMBER: 14648011 (USE FORMAT 7 OR 9 FOR FULL TEXT)

Aerosolised prostacyclin in adult respiratory distress syndrome.
Walmrath, Dieter; Schneider, Thomas; Pilch, Jan; Grimminger, Friedrich; Seeger, Werner
Lancet, v342, n8877, p961(2)
Oct 16, 1993
ISSN: 0099-5355 LANGUAGE: ENGLISH RECORD TYPE: FULLTEXT; ABSTRACT
WORD COUNT: 1509 LINE COUNT: 00129
ABSTRACT: Aerosolized prostacyclin is effective in the treatment of adult respiratory distress syndrome (ARDS). Aerosolized drug therapy is the administration of drugs that have been suspended in a fine mist. Prostacyclin is a vasodilating drug that causes blood vessels to stretch. ARDS is lung trauma resulting in difficult breathing. Three patients were given aerosolized prostacyclin in increasing doses. Decreased artery pressure in the patients indicated a decrease in pulmonary vascular resistance. This response lead to improved breathing.
AUTHOR ABSTRACT: We studied the effects of aerosolised prostacyclin ([PGI.sub.2]) in three patients with acute severe adult respiratory distress syndrome. 17-50 ng/kg per min, nebulised into the afferent limb of the ventilator circuit, decreased mean pulmonary artery pressure (SEM) from 40[multiplied by]3 (13[multiplied by]5) to 32[multiplied by]0 (3[multiplied by]8 (pulmonary vascular resistance fell by 30%); systemic arterial pressure decreased slightly from 76[multiplied by]8 (2[multiplied by]2) to 74[multiplied by]5 (6[mul mm Hg. Concomitantly, the ratio of arterial oxygen partial pressure to the fraction of inspired oxygen increased from 120 (19) to 173 (18), mainly due to redistribution of blood flow from shunt areas to regions of normal ventilation-perfusion. All effects were reversed on drug withdrawal. Lancet 1993; 342:/ 961-62

20/3,AB/9 (Item 6 from file: 148)
DIALOG(R)File 148:Gale Group Trade & Industry DB

06471985 SUPPLIER NUMBER: 13902009 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Preliminary study of the efficacy of insulin aerosol delivered by oral inhalation in diabetic patients.
Laube, Beth L.; Georgopoulos, Angeliki; Adams, G.K., III
JAMA, The Journal of the American Medical Association, v269, n16, p2106(4)
April 28, 1993
ISSN: 0098-7484 LANGUAGE: ENGLISH RECORD TYPE: FULLTEXT; ABSTRACT
WORD COUNT: 3618 LINE COUNT: 00303
ABSTRACT: Oral inhalation of aerosolized insulin may be effective in the treatment of patients with non-insulin dependent diabetes (NIDDM). Six non-obese, nonsmoking patients with NIDDM began insulin inhalation with approximately 1 Unit of insulin per kilogram of body weight. Fifty percent to 93% of the inhaled dose was deposited in the lungs of all six patients, and the average deposition below the larynx was 79%. Blood sugar levels significantly dropped in all six patients after insulin inhalation, and they dropped to within the normal range in five patients. The patients tolerated the aerosolized insulin well, and no adverse reactions, including coughing, were reported. Although further studies are needed, inhalation may prove to be a safe and simple alternative to the injection of insulin.
AUTHOR ABSTRACT: Objective.--To maximize deposition of an aerosolized dose of insulin (mean[+ or -] SD=0.99[+ or -]0.06 U/kg of body weight) in the lungs of subjects with non-insulin-dependent diabetes mellitus (NIDDM), and investigate its efficacy in normalizing plasma glucose levels during the fasting state.
Design.--Nonrandomized, placebo-controlled trial.
Setting.--A primary care facility.

Patients or Other Participants.--Six nonobese, nonsmoking volunteers with NIDDM. No subjects withdrew from the study.

Intervention.--Aerosolized insulin was administered by oral inhalation after a 12-hour period of fasting. Aerosol was generated by a raindrop nebulizer from regular 500 U/mL pork insulin. During inhalation , inspiratory flow was regulated at 17 L/min. Plasma samples were collected after inhalation and analyzed for insulin and glucose levels.

Main Outcome Measures.--Plasma insulin and glucose levels.

Results.--Deposition of the aerosol was maximized within the lungs, with 79% [+ or -] 17% of the inhaled dose depositing below the larynx. Geometric mean fasting plasma insulin level was 71 pmol/L (11.8 [micro]U/mL), rising to 269 pmol/L (44.8 [micro]U/mL) after insulin inhalation . Average time to peak insulin level was 40[+ or -]34 minutes. The mean fasting plasma glucose level (12.63[+ or -]2.59 mmol/L [225.5[+ or -]46.3 mg/dL]) was reduced to within the normal range in five subjects and was almost normal in the sixth subject (5.52[+ or -]0.89 mmol/L [98.6[+ or -]15.9 mg/dL]). Average maximum decrease in plasma glucose from baseline was 55%[+ or -]10% (n=6) vs 13%[+ or -]9% after placebo aerosol inhalation (n=3). No side effects were reported following insulin or placebo aerosol inhalation .

Conclusions.--These preliminary results indicate that a dose of approximately 1.0 U of aerosolized insulin per kilogram of body weight, delivered by oral inhalation and deposited predominantly within the lungs, is well tolerated and can effectively normalize plasma glucose levels in patients with NIDDM.

20/3,AB/12 (Item 9 from file: 148)
DIALOG(R)File 148:Gale Group Trade & Industry DB
(c)2001 The Gale Group. All rts. reserv.
03941426 SUPPLIER NUMBER: 07615735 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Allergy and immunology. (Contempo '89)
Lockey, Richard F.; Bukantz, Samuel C.
JAMA, The Journal of the American Medical Association, v261, n19, p2824(2)
May 19, 1989
ISSN: 0098-7484 LANGUAGE: ENGLISH RECORD TYPE: FULLTEXT
WORD COUNT: 1843 LINE COUNT: 00154

20/3,AB/17 (Item 1 from file: 484)
DIALOG(R)File 484:Periodical Abs Plustext
(c) 2001 ProQuest. All rts. reserv.
03640287 (USE FORMAT 7 OR 9 FOR FULLTEXT)
The use of albuterol in hospitalized infants with bronchiolitis
Dobson, Joseph V; Stephens-Groff, Susan M; McMahon, Shawn R; Stemmler, Margaret M; et al
Pediatrics (IPED), v101 n3 (Part 1), p361-368, p.8
Mar 1998
ISSN: 0031-4005 JOURNAL CODE: IPED
DOCUMENT TYPE: Feature
LANGUAGE: English RECORD TYPE: Fulltext; Abstract
WORD COUNT: 5697
ABSTRACT: Dobson et al examined whether the use of albuterol by nebulization enhances physiologic or clinical recovery in hospitalized infants with moderate bronchiolitis. They found that nebulized albuterol therapy does not appear to enhance recovery or attenuate severity of illness in infants hospitalized with acute, moderate bronchiolitis.

20/3,AB/18 (Item 1 from file: 149)

DIALOG(R)File 149:TGG Health&Wellness DB(SM)
(c) 2001 The Gale Group. All rts. reserv.
01900243 SUPPLIER NUMBER: 61635217 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Dose-Response to Inhaled Aerosolized Prostacyclin for Hypoxemia Due to ARDS(*).
van Heerden, P. Vernon; Barden, Anne; Michalopoulos, Nicholas; Bulsara, Max K.; Roberts, Brigit L.
Chest, 117, 3, 819
March, 2000
PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0012-3692
LANGUAGE: English RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 6415 LINE COUNT: 00561

20/6/21 (Item 4 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)
(c) 2001 The Gale Group. All rts. reserv.
01724770 SUPPLIER NUMBER: 19891694 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Interpretation of positive results of a methacholine inhalation challenge and 1 week of inhaled bronchodilator use in diagnosing and treating cough-variant asthma.

20/3,AB/22 (Item 5 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)
(c) 2001 The Gale Group. All rts. reserv.
01495141 SUPPLIER NUMBER: 15842365 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Acute bronchial and hematologic effects following inhalation of a single dose of PAF: comparison between asthmatics and normal subjects. (platelet activating factor)
Louis, Ranaud; Bury, Thierry; Corhay, Jean-Louis; Radermecker, Maurice F.
Chest, v106, n4, p1094(6)
Oct, 1994
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-3692 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 4399 LINE COUNT: 00376

20/3,AB/23 (Item 6 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)
(c) 2001 The Gale Group. All rts. reserv.
01431347 SUPPLIER NUMBER: 14636107 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Bronchoconstrictive responses to inhaled ultrasonically nebulized distilled water and airway inflammation in asthma.
Carpi, Sandro; Marini, Maurizio; Vittori, Enza; Vassalli, Giovanni; Mattoli, Sabrina
Chest, v104, n5, p1346(6)
Nov, 1993
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-3692 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 4178 LINE COUNT: 00363

20/3,AB/26 (Item 9 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)
(c) 2001 The Gale Group. All rts. reserv.
01357854 SUPPLIER NUMBER: 12185833 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Metered dose inhaler therapy for asthma, bronchitis, and emphysema.
Hofford, James M.
Journal of Family Practice, v34, n4, p485(8)
April, 1992
PUBLICATION FORMAT: Magazine/Journal ISSN: 0094-3509 LANGUAGE: English

RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 5635 LINE COUNT: 00489

24/6/26 (Item 2 from file: 149)
01682461 SUPPLIER NUMBER: 19261254 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Ciliary beat frequency in human bronchi and bronchioles.
1997
WORD COUNT: 3213 LINE COUNT: 00344

24/6/27 (Item 3 from file: 149)
01367668 SUPPLIER NUMBER: 12593792 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Validation of an exposure system to particles for the diagnosis of occupational asthma.
1992
WORD COUNT: 3345 LINE COUNT: 00351

File 350:Derwent WPIX 1963-2001/UD,UM &UP=200170
File 344:CHINESE PATENTS ABS APR 1985-2001/Oct
File 347:JAPIO OCT 1976-2001/Aug(UPDATED 011203)
File 371:French Patents 1961-2001/BOPI 200147

Set	Items	Description
S1	51452	INHAL????? OR AEROSOL? ?
S2	967535	PARTICLE? ? OR MIST OR POWDER??
S3	356	TAP()(DENSITY OR DENSITIES)
S4	2775	BIOACTIVE
S5	548497	RECEPTACLE? ? OR CONTAINER? ? OR NEBULI?ER? ? OR ATOMI?ER? ? OR VAPORI?ER? ?
S6	431692	DENSITY OR DENSITIES
S7	748294	TAP??? OR VIBRAT????
S8	6	S1 AND S2(5N)S3
S9	4147	VOLUME AND (CM3 OR CC OR CU()CM OR CUBIC()CENTIMET???)
S10	4	S1 AND S5 AND S9
S11	0	S8 AND S10
S12	**10**	**S8 OR S10**

12/26/2 (Item 2 from file: 350)
DIALOG(R)File 350:Derwent WPIX
(c) 2001 Derwent Info Ltd. All rts. reserv.
013883323 **Image available**
WPI Acc No: 2001-367536/200138
Dispenser for administering combination of drug and gas, comprises chamber charged from gas container, venturi and valves controlling operation

12/26,K/4 (Item 4 from file: 350)
DIALOG(R)File 350:Derwent WPIX
(c) 2001 Derwent Info Ltd. All rts. reserv.
013654021
WPI Acc No: 2001-138233/200114
A new method for delivering a therapeutic gas to a patient comprising infusing a nasal, oral or ocular mucous membrane with a flow of therapeutic gas
Abstract (Basic):
... or oral mucous membrane with the flow of therapeutic gas; where the patient refrains from inhaling the therapeutic gas...
...releasing from a hand-held dispenser a flow of therapeutic gas comprising 0.5-20 cc /second, when the gas is selected from CO2, NO, O, He, dilute mixtures of NO...

...a) a container holding a volume of the therapeutic gas under pressure...
...b) a flow regulator that releases a flow of the therapeutic gas from the container ; and...
...a) a container holding a volume of CO2 under pressure; and...
...b) a flow regulator that releases a flow of the CO2 from the container at a rate of 0.5-20 cc /second...
...a) a container holding a therapeutic gas; and...
...b) instructions for use for delivering the therapeutic gas to a patient from the container comprising...
...or oral mucous membrane with the flow of therapeutic gas, where the patient refrains from inhaling the therapeutic gas...
...a) a hand-held container holding CO2; and...
...b) instructions for use for delivering the CO2 from the container to a patient comprising releasing from the hand-held container a flow of CO2 comprising 0.5-20 cc /second of CO2...
...a) a container holding a therapeutic gas; and...
...b) instructions for use for delivering the therapeutic gas to a patient from the container comprising...
...The methods allows the delivery of a small volume of therapeutic gas of high concentration to provide faster relief without the adverse side effects of systemic drugs that are ingested, injected or inhaled .

12/26/5 (Item 5 from file: 350)
DIALOG(R)File 350:Derwent WPIX
(c) 2001 Derwent Info Ltd. All rts. reserv.
013134306 **Image available**
WPI Acc No: 2000-306177/200027
Gas-propelled aerosol dispenser has spherical container of thermoplastic material with vitreous transition temperature above 80 deg C

12/7/1 (Item 1 from file: 350)
DIALOG(R)File 350:Derwent WPIX
(c) 2001 Derwent Info Ltd. All rts. reserv.
014096983
WPI Acc No: 2001-581197/200165
Preparation of particulate drug-containing material (e.g. insulin), by mixing a drug-containing solution with an antisolvent, and encapsulating to form aerosolizable particles for inhalation
Patent Assignee: RXKINETIX INC (RXKI-N)
Inventor: ETTER J B
Number of Countries: 093 Number of Patents: 002
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200145731	A1	20010628	WO 2000US34436	A	20001218	200165	B
AU 200127291	A	20010703	AU 200127291	A	20001218	200165	

Priority Applications (No Type Date): US 2000604786 A 20000626; US 99469733 A 19991221
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200145731	A1	E	63	A61K-038/28	

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

AU 200127291 A A61K-038/28 Based on patent WO 200145731
Abstract (Basic): WO 200145731 A1

NOVELTY - Method for making a drug-containing particulate product comprises: (a) contacting a drug-containing feed solution (comprising the drug in a cosolvent system of at least 2 organic solvents) with a compressed anti-solvent fluid to precipitate drug-containing particles; and (b) separating the drug-containing particles from the anti-solvent fluid.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a particulate product for pulmonary delivery of a drug comprising a powder batch of particles including at least 1 drug. **The powder batch has a tap density of 0.1-0.5 g/cm3** and is aerosolizable by an inhaler to give an aerosol having dispersed drug particles of mass median aerodynamic diameter of less than 6 microns in a carrier gas;

(2) a method for generating an aerosol for pulmonary delivery of a drug by aerosolizing drug-containing particles;

(3) a particulate product comprising a multicomponent material including a drug and a biocompatible polymer and having a degree of drug encapsulation of at least 30%. The particulate product is aerosolizable by an inhaler to give an aerosol having dispersed drug particles of mass median aerodynamic diameter of less than 6 microns; and

(4) an apparatus for generating a drug-containing aerosol for pulmonary delivery, comprising an inhaler containing particulate material, the inhaler being able to aerosolize the particles to give a drug-containing aerosol .

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - None given.

USE - Drug-containing particles (especially containing insulin) are useful for aerosolizing in an inhaler , for treating diabetic patients.

pp; 63 DwgNo 0/20

Derwent Class: A96; B04; B07
International Patent Class (Main): A61K-038/28
International Patent Class (Additional): A61K-009/12; A61K-009/14; A61K-009/16; C07K-014/62; C07K-014/64

12/7/7 (Item 7 from file: 350)
DIALOG(R)File 350:Derwent WPIX

012975322
WPI Acc No: 2000-147171/200013
Aggregated particles for drug delivery to the pulmonary system comprise a therapeutic, diagnostic or prophylactic agent and a surfactant
Patent Assignee: ADVANCED INHALATION RES INC (ADIN-N)
Inventor: BATYCKY R P; CAPONETTI G; EDWARDS D A
Number of Countries: 086 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9966903	A2	19991229	WO 99US14074	A	19990622	200013	B
AU 9947068	A	20000110	AU 9947068	A	19990622	200025	
EP 1089712	A2	20010411	EP 99930552	A	19990622	200121	
			WO 99US14074	A	19990622		

Priority Applications (No Type Date): US 9890454 P 19980624
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes

WO 9966903 A2 E 68 A61K-009/12
Designated States (National): AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
AU 9947068 A A61K-009/12 Based on patent WO 9966903
EP 1089712 A2 E A61K-009/12 Based on patent WO 9966903
Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Abstract (Basic): WO 9966903 A2

NOVELTY - Aggregated particles for drug delivery to the pulmonary system include a therapeutic, diagnostic or prophylactic agent and a surfactant. **The particles have a tap density of less than 0.4 g/cm3**, a mean diameter of 5-30 microns and an aerodynamic diameter 1-3 or 3-5 microns.

DETAILED DESCRIPTION - **INDEPENDENT CLAIMS are also included for the following:**

(1) a method for **drug delivery to the pulmonary system comprising administering** to the **respiratory tract of a patient in need of treatment**, prophylaxis or diagnosis an amount of an invented aggregated particles and a material from surfactant or a molecule having a charge opposite to the charge of the agent to form a complex; and

(2) aggregated particles for drug delivery to the pulmonary system with an aerodynamic diameter of 3-5 microns and including particles comprising a charged therapeutic, diagnostic or prophylactic agent and a molecule with a charge opposite to that of the agent, forming a complex, the particles having a tap density of 0.4g/cm3, a mean diameter of 3-30micro-m and an aerodynamic diameter of 1-3microns.

ACTIVITY - None given.

MECHANISM OF ACTION - None given.

USE - The aggregated particles are used for drug delivery, and to deliver diagnostic agent to the pulmonary system (claimed).

ADVANTAGE - The invention has inhaled aerosols that are effective carriers for delivery of therapeutic agents to the deep lung. These carriers avoid phagocytosis in the deep lung and are capable of biodegrading and releasing the drug at a controlled rate. The particles have improved aerosolization properties and optimized particle-particle interactions.

pp; 68 DwgNo 0/11

Derwent Class: B05; B07
International Patent Class (Main): A61K-009/12

12/7/8 (Item 8 from file: 350)
DIALOG(R)File 350:Derwent WPIX

011996881
WPI Acc No: 1998-413791/199835
Particulate composition for inhalation - is especially suitable for sustained delivery of insulin
Patent Assignee: MASSACHUSETTS INST TECHNOLOGY (MASI); PENN STATE RES FOUND (PENN-N)
Inventor: CHEN D; EDWARDS D A; EVORA C; HANES J; LANGER R S; MINTZES J; VANBEVER R; WANG J; LANGER R
Number of Countries: 021 Number of Patents: 005
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9831346	A1	19980723	WO 97US20930	A	19971117	199835	B
US 5855913	A	19990105	US 97784421	A	19970116	199909	
EP 954282	A1	19991110	EP 97947545	A	19971117	199952	
			WO 97US20930	A	19971117		
US 5985309	A	19991116	US 97784421	A	19970116	200001	
			US 9759004	A	19970915		
			US 97971791	A	19971117		
US 37053	E	20010213	US 96655570	A	19960526	200111	
			US 96739308	A	19961029		
			US 97784421	A	19970116		
			US 99351341	A	19990712		

Priority Applications (No Type Date): US 9759004 P 19970915; US 97784421 A 19970116; US 97971791 A 19971117; US 96655570 A 19960526; US 96739308 A 19961029; US 99351341 A 19990712

Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9831346	A1	E	64	A61K-009/12	
Designated States (National): CA JP					
Designated States (Regional): AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
US 5855913	A			A61K-009/14	
EP 954282	A1	E		A61K-009/12	Based on patent WO 9831346
Designated States (Regional): AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
US 5985309	A			A61K-013/00	Cont of application US 97784421 Provisional application US 9759004
US 37053	E			A61K-009/14	CIP of application US 96655570 CIP of application US 96739308 Reissue of patent US 5855913 CIP of patent US 5874064

Abstract (Basic): WO 9831346 A

A particulate composition for drug delivery to the pulmonary system comprises biocompatible particles incorporating a therapeutic agent and a surfactant. The **particles have a tap density of < 0.4 g/cm3** and a mean diameter of 5-30 mu m effective to yield an aerodynamic diameter of 1-5 mu m.

Preferably at least 50% of the particles have an aerodynamic diameter of 3-5 mu m and a tap density of < 0.2 g/cm3. The therapeutic agent is preferably a protein, polysaccharide, lipid, nucleic acid nucleotide and/or oligonucleotide, especially insulin, calcitonin, leuprolide, granulocyte colony-stimulating factor, parathyroid hormone-related peptide, somatostatin, testosterone, progesterone, oestradiol, nicotine, fentanyl, norestherone, clonidine, scopolamine, salicylate, cromolyn sodium, salmeterol, formeterol, valium or albuterol. The surfactant is preferably a fatty acid, phospholipid or block copolymer, especially L- alpha -phosphatidylcholine dipalmitoyl.

ADVANTAGE - The composition is useful for delivering sustained serum insulin concentrations for at least 24 hours.

Dwg.0/8

Derwent Class: B04; B05; B07

International Patent Class (Main): A61K-009/12; A61K-009/14; A61K-013/00

International Patent Class (Additional): A61K-009/00; A61K-009/16; A61K-031/135; A61K-038/09; A61K-038/23; A61K-038/28; A61K-047/14; A61K-047/48

12/7/9 (Item 9 from file: 350)

DIALOG(R)File 350:Derwent WPIX

011601067
WPI Acc No: 1998-018195/199802
Aerodynamically light particles for pulmonary drug delivery - preferably comprise functionalised polyester graft copolymer with linear alpha-hydroxy acid polyester backbone containing aminoacid
Patent Assignee: MASSACHUSETTS INST TECHNOLOGY (MASI); PENN STATE RES FOUND (PENN-N); PENN RES FOUND INC (PENN-N); PENN RES FOUND (PENN-N)
Inventor: BEN-JEBRIA A A; CAPONETTI G; EDWARDS D A; HANES J; HRKACH J S; LANGER R S; LOTAN N; BEN-JEBRIA A
Number of Countries: 021 Number of Patents: 009
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
WO 9744013	A1	19971127	WO 97US8895	A	19970523	199802 B
US 5874064	A	19990223	US 96655570	A	19960524	199915
			US 96739308	A	19961029	
EP 907356	A1	19990414	EP 97927754	A	19970523	199919
			WO 97US8895	A	19970523	
JP 2000511189	W	20000829	JP 97542820	A	19970523	200045
			WO 97US8895	A	19970523	
US 6136295	A	20001024	US 96655570	A	19960524	200055
			US 96739308	A	19961029	
			US 98211940	A	19981215	
US 6254854	B1	20010703	US 96655570	A	19960524	200140
			US 2000569153	A	20000511	
US 20010033828	A1	20011025	US 96655570	A	19960524	200170
			US 2000569153	A	20000511	
			US 2001888688	A	20010625	
US 20010033829	A1	20011025	US 96655570	A	19960524	200170
			US 2000569153	A	20000511	
			US 2001888781	A	20010625	
US 20010033830	A1	20011025	US 96655570	A	19960524	200170
			US 2000569153	A	20000511	
			US 2001891131	A	20010625	

Priority Applications (No Type Date): US 96739308 A 19961029; US 96655570 A 19960524; US 98211940 A 19981215; US 2000569153 A 20000511; US 2001888688 A 20010625; US 2001888781 A 20010625; US 2001891131 A 20010625
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9744013	A1	E	45	A61K-009/00	
Designated States (National): CA JP US					
Designated States (Regional): AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
US 5874064	A			A61K-009/12	CIP of application US 96655570
EP 907356	A1	E		A61K-009/00	Based on patent WO 9744013
Designated States (Regional): AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 2000511189	W		43	A61K-009/14	Based on patent WO 9744013
US 6136295	A			A61L-009/04	CIP of application US 96655570
					Div ex application US 96739308
					Div ex patent US 5874064
US 6254854	B1			A61K-009/12	Cont of application US 96655570
US 20010033828	A1			A61K-038/28	Cont of application US 96655570
					Cont of application US 2000569153
					Cont of patent US 6254854
US 20010033829	A1			A61K-038/28	Cont of application US 96655570
					Cont of application US 2000569153

Cont of patent US 6254854
US 20010033830 A1 A61K-038/28 Cont of application US 96655570
Cont of application US 2000569153
Cont of patent US 6254854

Abstract (Basic): WO 9744013 A

A system for delivery to the pulmonary system comprises biodegradable particles with a tap density < 0.4 g/cm3, where at least 50% of particles have mass mean diameter (MMD) 5-30 mu m.

Also claimed are: (1) delivery of the above aerodynamically light particles to the pulmonary system by administration to the respiratory tract; and (2) preparation of particles comprising a functionalised polyester graft copolymer with a linear alpha -hydroxy acid polyester backbone having at least 1 amino acid incorporated; and at least 1 poly(amino acid) side chain extending from an aminoacid group in the polyester backbone, for administration to the respiratory tract by aerosolisation, by a solvent evaporation process.

USE - The particles can incorporate a therapeutic or diagnostic agent, and can be used to deliver it systemically or locally to the airways or alveolar region of the lung, (e.g. genes for treatment of cystic fibrosis, or beta agonists for asthma).

The particles containing an incorporated imaging agent may be used for a variety of diagnostic applications, including detecting and characterising tumour masses and tissues.

ADVANTAGE - The greater efficiency or aerosolisation by aerodynamically light particles of relatively large size permits more of an incorporated agent to be delivered than is possible with the same mass of relatively dense aerosols . The relatively large size also minimises potential drug losses caused y particle phagocytosis.

When the particles are formed from biocompatible polymers, the system can provide controlled release in the lungs and long-time local action or systemic bioavailability of the incorporated element.

Denaturation of macromolecular drugs can be minimised during aerosolisation since macromolecules are contained and protected within a polymeric shell. The enzymatic degradation of proteins or peptides can be minimised by co-incorporating peptidase inhibitors.

Dwg.0/7

Derwent Class: A23; A96; B04; B07; P32; P34
International Patent Class (Main): A61K-009/00; A61K-009/12; A61K-009/14; A61K-038/28; A61L-009/04
International Patent Class (Additional): A61F-002/00; A61K-031/715; A61K-047/32; A61K-048/00

File 348:EUROPEAN PATENTS 1978-2001/NOV W04
File 349:PCT FULLTEXT 1983-2001/UB=20011129,UT=20011122

Set	Items	Description
S1	59527	INHAL????? OR AEROSOL? ?
S2	283362	PARTICLE? ? OR MIST OR POWDER??
S3	314	TAP()(DENSITY OR DENSITIES)
S4	6447	BIOACTIVE
S5	170502	RECEPTACLE? ? OR CONTAINER? ? OR NEBULI?ER? ? OR ATOMI?ER? ? OR VAPORI?ER? ?
S6	200399	DENSITY OR DENSITIES
S7	209234	TAP??? OR VIBRAT????
S8	20	S1 AND S2(5N)S3
S9	43114	VOLUME AND (CM3 OR CC OR CU()CM OR CUBIC()CENTIMET???)
S10	3090	S1 AND S5 AND S9

S11 10 S8 AND S10
S12 3100 S8 OR S10
S13 544 S1 AND S5(S)S9
S14 2 S8 AND S13 [not relevant]
S15 18 S8 NOT S14
S16 18 IDPAT (sorted in duplicate/non-duplicate order)
S17 17 IDPAT (primary/non-duplicate records only)

17/TI/4 (Item 4 from file: 349)
DIALOG(R)File 349:(c) 2001 WIPO/Univentio. All rts. reserv.
SLOW RELEASE PROTEIN POLYMERS

17/TI/5 (Item 5 from file: 349)
DIALOG(R)File 349:(c) 2001 WIPO/Univentio. All rts. reserv.
PARTICULATE DRUG-CONTAINING PRODUCTS AND METHOD OF MANUFACTURE

17/TI/6 (Item 6 from file: 349)
DIALOG(R)File 349:(c) 2001 WIPO/Univentio. All rts. reserv.
USE OF SIMPLE AMINO ACIDS TO FORM POROUS PARTICLES

17/TI/7 (Item 7 from file: 349)
DIALOG(R)File 349:(c) 2001 WIPO/Univentio. All rts. reserv.
LARGE POROUS PARTICLES BY SPRAY-DRYING

17/TI/9 (Item 9 from file: 349)
DIALOG(R)File 349:(c) 2001 WIPO/Univentio. All rts. reserv.
POROUS DRUG MATRICES AND METHODS OF MANUFACTURE THEREOF

17/TI/10 (Item 10 from file: 349)
DIALOG(R)File 349:(c) 2001 WIPO/Univentio. All rts. reserv.
IMPROVEMENTS IN OR RELATING TO POWDERS

17/TI/11 (Item 11 from file: 349)
DIALOG(R)File 349:(c) 2001 WIPO/Univentio. All rts. reserv.
STABLE SPRAY-DRIED PROTEIN FORMULATIONS

17/TI/15 (Item 15 from file: 349)
DIALOG(R)File 349:(c) 2001 WIPO/Univentio. All rts. reserv.
PREPARATION OF POWDER AGGLOMERATES

17/3,AB/8 (Item 8 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT
(c) 2001 WIPO/Univentio. All rts. reserv.
00780762
MODULATION OF RELEASE FROM DRY POWDER FORMULATIONS
MODULATION DE LIBERATION A PARTIR DE FORMULATIONS SECHES EN POUDRE
Patent Applicant/Assignee:
ADVANCED INHALATION RESEARCH INC, 840 Memorial Drive, Cambridge, MA 02139, US, US (Residence), US (Nationality), (For all designated states except: US
Patent Applicant/Inventor:
BASU Sujit K, 20 Concord Avenue, No. 101, Cambridge, MA 02138, US, US (Residence), IN (Nationality), (Designated only for: US)
HRKACH Jeffrey S, 24 Cambridge Terrace, Cambridge, MA 02139, US, US (Residence), US (Nationality), (Designated only for: US)
CAPONETTI Giovanni, 807 Somerville Avenue, Somerville, MA 02143, US, US (Residence), IT (Nationality), (Designated only for: US)

LIPP Michael M, 1015 Southern Artery, No. 302, Quincy, MA 02169, US, US (Residence), US (Nationality), (Designated only for: US)
ELBERT Katharina, 29 Concord Avenue, No. 101, Cambridge, MA 02138, US, US (Residence), DE (Nationality), (Designated only for: US)
LI Wen-I, 32 James Street, Lexington, MA 02420, US, US (Residence), -- (Nationality), (Designated only for: US)
Legal Representative:
ELMORE Carolyn S (et al) (agent), Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02421, US,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200113891 A2-A3 20010301 (WO 0113891)
Application: WO 2000US23048 20000823 (PCT/WO US0023048)
Priority Application: US 99150742 19990825
Designated States: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
(EP) AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
(OA) BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 12479
English Abstract
Particles which include a bioactive agent are prepared to have a desired matrix transition temperature. Delivery of the particles via the pulmonary system results in modulation of drug release from the particles. Sustained release of the drug can be obtained by forming particles which have a high matrix transition temperature, while fast release can be obtained by forming particles which have a low matrix transition temperature. Preferred particles include one or more phospholipids.

17/3,AB/14 (Item 14 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

00472102
BIODEGRADABLE MACROMERS FOR THE CONTROLLED RELEASE OF BIOLOGICALLY ACTIVE SUBSTANCES
MACROMERES BIODEGRADABLES PERMETTANT DE LIBERER DE MANIERE REGULEE DES SUBSTANCES BIOLOGIQUEMENT ACTIVES
Patent Applicant/Assignee:
INFIMED INC,
Inventor(s):
HUBBELL Jeffrey A,
KIERAS Mark T,
RON Eyal S,
ROWE Stephen C,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9903454 A1 19990128
Application: WO 98US14723 19980717 (PCT/WO US9814723)
Priority Application: US 9753029 19970718
Designated States: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH

CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 14775
English Abstract
A method for delivering a biologically active substance including the steps of: (a) combining said biologically active substance with a macromer; (b) forming a mixture of the combination formed in step (a); (c) polymerizing said mixture to form articles; and (d) administering said articles, or a portion thereof, to a mammal, where step (c) takes place in the absence of a polymerizable monovinyl monomer, is disclosed.

17/3,AB/16 (Item 16 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

00440882
PREPARATION OF PARTICLES FOR INHALATION
PREPARATION DE PARTICULES POUR INHALATION
Patent Applicant/Assignee:
MASSACHUSETTS INSTITUTE OF TECHNOLOGY,
THE PENN STATE RESEARCH FOUNDATION,
Inventor(s):
EDWARDS David A,
HANES Justin,
EVORA Carmen,
LANGER Robert S,
VANBEVER Rita,
MINTZES Jeffrey,
WANG Jue,
CHEN Donghao,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9831346 A1 19980723
Application: WO 97US20930 19971117 (PCT/WO US9720930)
Priority Application: US 97421 19970116; US 9759004 19970915
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English Abstract
Particles incorporating a surfactant and/or a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a charged molecule of opposite charge for drug delivery to the pulmonary system, and methods for their synthesis and administration are provided. **In a preferred embodiment, the particles are made of a biodegradable material and have a tap density less than 0.4 g/cm3** and a mass mean diameter between 5 'mu'm and 30 'mu'm, which together yield an aerodynamic diameter of the particles of between approximately one and three microns. The particles may be formed of biodegradable materials such as biodegradable polymers. For example, the particles may be formed of poly(lactic acid) or poly(glycolic acid) or copolymers thereof. Alternatively, the particles may be formed solely of a therapeutic or diagnostic agent and a surfactant. Surfactants can be incorporated on the particule surface for example by coating the particle after particle formation, or by incorporating the surfactant in the material forming the particle prior to formation of the particle. Exemplary surfactants include phosphoglycerides such as dipalmitoyl phosphatidylcholine (DPPC). The particles can be effectively aerosolized for administration to the respiratory tract to permit systemic or local delivery of wide a variety

of therapeutic agents. Formation of complexes of positively or negatively charged therapeutic agents with molecules of opposite charge can allow control of the release rate of the agents into the blood stream following administration.

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DIALOG(R)File 349:PCT FULLTEXT

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AERODYNAMICALLY LIGHT PARTICLES FOR PULMONARY DRUG DELIVERY
PARTICULES LEGERES AERODYNAMIQUES POUR LA DIFFUSION DE MEDICAMENTS DANS L'APPAREIL RESPIRATOIRE
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Patent: WO 9744013 A1 19971127
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English Abstract
Improved aerodynamically light particles for delivery to the pulmonary system, and methods for their preparation and administration are provided. **In a preferred embodiment, the aerodynamically light particles are made of a biodegradable material and have a tap density less than 0.4 g/cm3** and a mass mean diameter between 5 'mu'm and 30 'mu'm. The particles may be formed of biodegradable materials such as biodegradable polymers. For example, the particles may be formed of a functionalized polyester graft copolymer consisting of a linear 'alpha'-hydroxy-acid polyester backbone having at least one amino acid group incorporated therein and at least one poly(amino acid) side chain extending from an amino acid group in the polyester backbone. In one embodiment, aerodynamically light particles having a large mean diameter, for example greater than 5 'mu'm, can be used for enhanced delivery of a therapeutic or diagnostic agent to the alveolar region of the lung. The aerodynamically light particles optionally can incorporate a therapeutic or diagnostic agent, and may be effectively aerosolized for administration to the respiratory tract to permit systemic or local delivery of wide variety of incrorporated agents.

Chemical Abstracts Database

(FILE 'HOME' ENTERED AT 13:24:28 ON 04 DEC 2001)
FILE 'HCAPLUS' ENTERED AT 13:24:33 ON 04 DEC 2001

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L1        55072 S AEROSOL?
L2           60 S TAP(W)(DENSITY OR DENSITIES)
L3        12912 S BIOACTIVE
L4         1584 S S1 AND S2 AND S3
L5      1174937 S PARTICLE? OR MIST? OR POWDER
L6            0 S L1 AND L2 AND L3
L7            4 S L1 AND L2
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L7 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:109578 HCAPLUS duplicate
DN 135:24556
TI Influence of formulation excipients and physical characteristics of inhalation dry powders on their ***aerosolization*** performance

L7 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:147131 HCAPLUS duplicate
DN 132:284178
TI Sustained release of insulin from insoluble inhaled particles

L7 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:725322 HCAPLUS
DN 132:54774
TI Formulation and physical characterization of large porous particles for inhalation duplicate

L7 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2001 ACS duplicate
AN 1999:133203 HCAPLUS
DN 130:200926
TI Aerodynamically light particles for pulmonary drug delivery